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ABSTRACT

Title of Dissertation: Biobehavioral Triggers of Cardiac Arrhythmia during Daily Life: The Role of Emotion, Physical Activity, and Heart Rate Variability

Melissa K. McCeney, Doctor of Philosophy, 2004

Dissertation directed by: David S. Krantz, Ph.D.
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ABSTRACT

Biobehavioral factors, such as physical activity and emotions, have been associated with adverse cardiac outcomes, including myocardial ischemia and infarction, in individuals with coronary artery disease. However, cardiac arrhythmia has largely been neglected with regard to psychosocial influences. The present study examined the role of physical activity and acute emotions in triggering arrhythmia in susceptible individuals during everyday activities. In addition, it addressed the impact of chronic factors, including trait anxiety, hostility, depression, and usual levels of physical activity on arrhythmia. Finally, this research explored short-term and long-term heart rate variability (HRV) as a potential mechanism for the impact of biobehavioral factors on cardiac arrhythmia.

Participants included 40 men and 10 women with documented coronary artery disease who have received implantable cardioverter defibrillators (ICDs). As part of the Triggers of Arrhythmia in Defibrillator Patients (TRIAD) study, these individuals were monitored for 48

hours using ambulatory electrocardiogram (ECG) recorders. During the monitoring period, participants completed two structured diaries, recording their activities and moods. Participants also completed standardized measures of depression, hostility, and trait anxiety.

Ambulatory ECG tapes were analyzed to identify arrhythmic events, and these events were correlated with changes in physical activity and/or emotions to identify acute triggers of arrhythmia. Acute changes in HRV immediately coincident and following these triggers were evaluated. Long-term HRV and chronic factors were be correlated with arrhythmia.

As predicted, higher levels of trait anxiety and chronic depressive symptoms were associated with lower measures of heart rate variability. Although all associations between hostility and HRV were negative (i.e., higher hostility was associated with lower HRV), the associations were small and did not reach statistical significance.

Participants appeared to have been more likely to be exposed to acute negative emotions prior to more severe cardiac arrhythmia, such as bigeminy, triplets, and ventricular runs, compared to control periods when no arrhythmia occurred. This association was not present when couplets were included in the analyses.

In the present sample, HRV did not change significantly prior to arrhythmic events. However, nonsignificant changes were consistently in the predicted direction (decreasing prior to arrhythmias). The changes in HRV prior to more severe arrhythmias, particularly ventricular runs, were considerably larger than those prior to more benign arrhythmias (such as couplets), but the small number of more severe arrhythmias experienced by the present sample prevented those changes from reaching statistical significance.

Surprisingly, participants were less likely to have been exposed to acute physical activity

prior to arrhythmia than during control periods when no arrhythmia occurred. This finding is likely due to the fact that patients didn't feel well prior to arrhythmias and therefore chose not to be physically active at that time. Although they did not report increased chest pain or shortness of breath prior to arrhythmias, there was no measure of general malaise, and patients were significantly more likely to report feeling tired prior to arrhythmias compared to control periods.

Further, higher depressive symptoms were unexpectedly associated with fewer arrhythmias. This disparate finding may be due to a type of selection bias due to the length of time that had passed since participants had their first infarct and the length of time that had passed since their ICDs were implanted. Given the low levels of depressive symptoms in this sample, this finding may also reflect a maladaptive level of unrealistic optimism. Further study is necessary to determine the role of unrealistic optimism in cardiovascular outcomes. Neither hostility nor trait anxiety was associated with cardiac arrhythmia.

Self-reported usual levels of light, vigorous, heavy, and extreme physical activity were not significantly associated with any type of arrhythmia. However, nonsignificant correlations were all in the predicted direction; that is, more frequent heavy and extreme activity were associated with fewer arrhythmias. Unexpectedly, higher levels of moderate activity were significantly associated with more frequent arrhythmias, which may indicate that the acute risk of physical activity outweighs the benefit of consistent activity. It may also be that participants in the present sample did not exercise frequently enough for physical activity to be beneficial. It is unclear whether self-reported usual levels of physical activity adequately reflect physical fitness levels. However, correlations between reported activity levels, resting heart rate, and body mass index suggest that they do reflect physical fitness, at least to some extent. Additional research

using more objective measures of physical fitness, such as aerobic capacity and cardiovascular endurance, may help to clarify these findings. Usual levels of physical activity were not associated with any measure of heart rate variability.

Contrary to predictions, heart rate variability did not change following negative emotions, perhaps due to low baseline levels of HRV that did not allow for much fluctuation. This finding may help to explain why exposure to acute negative emotions did not increase the risk of arrhythmia.

Measures of 24-hour HRV were not associated with the frequency of arrhythmias in the present sample, which may reflect the lack of an association between HRV and arrhythmia in ICD patients, but may also be the result of lingering effects of beta-blockers.

Biobehavioral Triggers of Cardiac Arrhythmia during Daily Life:

The Role of Emotion, Physical Activity, and Heart Rate Variability

by

Melissa K. McCeney

Dissertation submitted to the Faculty of the Department of Medical and Clinical Psychology Graduate Program of the Uniformed Services University of the Health Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 2004

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INTRODUCTION

Coronary artery disease (CAD) refers to a set of conditions resulting from the accumulation of plaque in coronary arteries (i.e., coronary atherosclerosis.) Coronary artery disease may lead to chest pain as a result of insufficient blood flow to the heart (myocardial ischemia), myocardial infarction (heart attack), and sudden death resulting from disruption in the heart's normal rhythm (arrhythmia).

Cardiovascular disease has been the number one killer in the United States for 99 of the last 100 years (American Heart Association, 2001). In 1999, cardiovascular disease claimed the lives of nearly one million people, and nearly 2,600 Americans die of cardiovascular disease every day. Cardiovascular disease claims almost as many lives each year as the next seven leading causes of death combined, and 33% of people who die of heart disease die prematurely (i.e., before their average life expectancy). Nearly 150,000 people who die of cardiovascular disease each year are under age 65 (American Heart Association, 2001).

Because cardiovascular disease has a tremendous impact on U.S. public health, it is of utmost importance to determine causes of CAD development and progression in order to prevent CAD morbidity and mortality. Although a number of physiological risk factors have been identified (hypertension, hyperlipidemia, etc; American Heart Association, 2001), a substantial proportion of the variance in morbidity and mortality remains unexplained. The last few decades have seen psychological and behavioral factors come under scrutiny as possible influences. There is now evidence that psychological factors influence the development of atherosclerosis (e.g., Barefoot, Dahlstrom & Williams, 1983), as well as clinical manifestations of CAD, such as

myocardial ischemia (e.g., Krantz, Kop, Santiago & Gottdiener, 1996) and myocardial infarction (e.g., Mittleman, Maclure, Sherwood, Mulry, Tofler et al., 1995).

Preliminary evidence suggests that behavioral factors, including physical and mental activities, may also influence the incidence of cardiac arrhythmia in vulnerable individuals (e.g., James et al., 2000). There is also preliminary evidence that negative emotions and physical activity may play a role in cardiac arrhythmia (e.g., Verrier & Mittleman, 1996). However, these triggering events and the nature of pathophysiological mechanisms are still poorly understood. Evidence also suggests that negative emotions may be associated with reduced heart rate variability (HRV; e.g., Grossman et al., 1990), and that HRV is associated with arrhythmia (e.g., Lanza et al., 1999). The present study focuses on the role of acute and chronic emotions and physical activity as predictors of reduced heart rate variability and arrhythmia in susceptible patients with CAD and a low threshold for cardiac arrhythmias (i.e., patients with an implantable cardioverter defibrillator). The following sections will address: (1) behavioral factors in CAD, differentiating acute versus chronic psychological risk factors; (2) biobehavioral factors and cardiac arrhythmia; (3) ecological momentary assessment of psychological risk factors; (4) the case-crossover design for the investigation of behavioral cardiovascular risk factors; and (5) the study aims and hypotheses of this research project. These background sections are followed by a detailed description of the methodology and results related to behavioral factors in cardiac arrhythmias. The results will be discussed in the last section of this dissertation with emphases on integration with the current literature, potential study limitations, and direction for future research in cardiovascular behavioral medicine in high-risk patients with CAD.

1. Biobehavioral Factors and Coronary Artery Disease

It has long been believed that acute exercise may result in clinical manifestations of CAD (e.g., Mittleman, et al., 1993), but more recent evidence suggests that other behavioral factors, including mental stress, sexual activity, and acute emotions may also trigger coronary events (e.g., Gabbay, et al., 1996; Drory, et al., 1995; Verrier & Mittleman, 1996). Research regarding the effects of behavioral factors and triggers on the development and manifestations of cardiovascular disease has thus far largely focused on myocardial ischemia and infarction.

Ischemia is an important determinant of life-threatening cardiac arrhythmias. The following review will therefore first examine the literature on behavioral factors and cardiac ischemia, after which behavioral aspects of the main cardiac end point of this project (arrhythmias) will be addressed.

Cardiac arrhythmias account for as many as 500,000 deaths and 761,000 hospital admissions per year. In addition, health care costs associated with arrhythmia are estimated to be over $2 billion per year (American Heart Association, 2001). Therefore, the present study will focus on cardiac arrhythmia. This literature review will first examine prior work exploring myocardial ischemia and infarction, and will then review the much smaller body of knowledge regarding biobehavioral factors and arrhythmia that exists to date. The ways in which what is currently known about ischemia may apply to arrhythmia will also be discussed.

Acute versus chronic risk factors. Biobehavioral factors that affect the manifestations of coronary heart disease generally fall into one of three categories: acute stress, chronic

environmental factors, and psychological traits. It is important to make the distinction between chronic and acute risk factors (Muller, et al., 1994). Chronic risk factors are longstanding and influence the development or progression of coronary disease over a period of time. Chronic physiological risk factors include elevated LDL cholesterol, smoking, obesity, and hypertension, all of which contribute to atherosclerosis over time. Similarly, chronic environmental factors and psychological traits are longstanding and impact the cardiovascular system over time.
Acute risk factors are transient pathophysiological changes resulting from external factors, such as physical exercise or acute mental stress. Acute factors do not necessarily contribute to the development of chronic disease, but instead may trigger clinical events, such as myocardial ischemia, myocardial infarction, and sudden death, among individuals who already have CAD. Acute and chronic risk factors are hypothesized to combine to increase the risk of clinical cardiac events. Acute risk factors are often "triggered" by patient behaviors. Chronic risk factors serve to form a base level of risk, which may decrease the severity of the acute risk factor needed in order to elicit an event.

A third category, episodic risk factors, refers to behavioral characteristics, such as depression, that are neither acute nor chronic, but range in duration from several months to several years (Kop, 1999). The concepts of acute, chronic, and episodic risk factors help to explain the otherwise unpredictable timing of coronary events.

The role of triggers in cardiac events. Until the early 1980s, acute cardiac events, such as myocardial infarction and sudden death, were generally seen as random, unpredictable events. However, given current knowledge that clinical events are more likely to occur during the morning hours after awakening (e.g., DeWood, Spores, Notske, Mouser, Burroughs, Golden, et

al., 1980), and greater understanding of physiological events that precede acute clinical events, such as myocardial ischemia, many cardiologists now subscribe to the hypothesis that clinical events can be triggered by patient behavior and/or transient physiological changes.

According to a model proposed by Muller and colleagues (1994), physical and mental activities of the patient may elicit physiological changes that precipitate clinical events. These behaviors are described as "triggers." The physiological changes they elicit are considered to be acute risk factors for adverse cardiac events. The process is as follows:

Triggering event - A patient's behavior produces acute physiologic or pathophysiologic changes leading directly to the onset of acute manifestations of CAD, such as myocardial ischemia or infarction. The behavior is called a trigger.

Acute risk factor – Triggers produce one or more acute risk factors; that is, transient physiological changes that may trigger disease onset, such as an increase in coagulability or vasoconstriction.

Vulnerable atherosclerotic plaque - A vulnerable atherosclerotic plaque is a lesion, not necessarily stenotic, that has a high likelihood of becoming disrupted and forming a thrombogenic focus after exposure to an acute risk factor.

Non-fatal myocardial infarction or sudden cardiac death – An acute risk factor that occurs in the presence of a vulnerable atherosclerotic plaque may lead to myocardial infarction or other clinical manifestations of CAD (Muller, Abela, Nesto & Tofler, 1994).

The concept of triggering is important because, if clinical manifestations of CAD can be predicted (and possibly controlled) based on patient behaviors that have been identified as

increasing the likelihood of adverse physiological changes, lives may be saved. Most cardiovascular deaths occur suddenly before any treatment can be initiated (Muller & Tofler, 1991). Identifying, and subsequently blocking, the acute processes triggering onset of manifestations of CAD may ultimately reduce the number of cardiac deaths each year (Muller, Abeal, Nesto & Tofler, 1994).

Although Muller's model of triggers focuses primarily on myocardial infarction, the concept could also be applied to cardiac arrhythmia. A patient behavior may lead to an acute risk factor, such as autonomic changes that lead to reduced heart rate variability. In the presence of vulnerable cardiac substrate, such as myocardial tissue that has been damaged by prior infarction, those autonomic changes could ultimately result in arrhythmia.

Acute Risk Factors

Acute physical activity. Physical activity that results in increased heart rate would seem to be an obvious trigger for cardiac events because increased physical activity increases metabolic demand on myocardial tissue. Among CAD patients, manifestations of the disease may result in an inadequate supply of oxygen. Laboratory studies confirm this intuitive hypothesis. For example, in a study of 55 patients with documented CAD, myocardial perfusion was evaluated using thallium-201 imaging. All 55 patients experienced myocardial ischemia during exercise testing. Twenty-seven of these patients demonstrated myocardial hypoperfusion in the absence of chest pain during exercise. The remaining patients also showed hypoperfusion upon exercising, but did experience angina. During the 30-month follow-up period, six of the patients with silent ischemia experienced a subsequent heart attack with three fatalities. Only one

patient among those who had chest pain had a subsequent, nonfatal infarction, suggesting that silent exercise-induced ischemia may have even more prognostic value than that associated with pain (Assey, Walters, Hendrix, Carabello Usher, & Spann, 1987).

Acute physical activity has been shown to trigger myocardial infarction during daily life, as well (Maclure, 1991). In the early 1990s, while the capacity of exercise to induce ischemia was well-established in the laboratory (e.g., Assey, Walters, Hendrix, Carabello, Usher & Spann, 1987), no one had yet conducted a controlled study to determine whether acute physical activity confers increased risk of infarction or the length of time between exertion and onset of symptoms. To more systematically examine the role of triggers in cardiac outcomes, Maclure (1991) developed a novel epidemiologic methodology, called the case crossover design, that compares each patient's activities prior to myocardial infarction to his or her usual level of activities to assess the immediate physical and mental triggers of infarct onset. Using the case-crossover design, Mittleman and colleagues interviewed 1228 patients following their first myocardial infarction to determine the time, type, and intensity of any physical exertion that occurred in the 26 hours prior to infarct. Of those patients, 4.4% reported having engaged in heavy physical activity (defined as 6 metabolic equivalents or more) prior to the onset of symptoms. The relative risk of infarct following heavy exertion was 5.9 compared to that following less strenuous exertion or no exertion. Symptoms typically appeared within less than 1 hour following the strenuous activity, and often began during the activity (Mittleman, Maclure, Tofler, Sherwood, Goldberg, & Muller, 1993).

The propensity of physical activity to induce ischemia has been confirmed during ambulatory studies, as well. A study of 63 stable coronary artery disease patients utilized ambulatory electrocardiogram (ECG) monitors to evaluate transient myocardial ischemia,

defined as horizontal or downsloping ST-segment depression greater than 1 millimeter for at least 60 seconds. Participants recorded their activities throughout the day in previously validated structured diaries. Analyses revealed that strenuous physical activity significantly increased the risk of ischemia during the morning hours, and to a lesser degree, during the evening hours. However, high levels of physical activity did not predict ischemia during the afternoon hours (Krantz, Kop, Gabbay, Rozanski, Barnard, et al., 1996).

Acute mental stress. Mental stress is another such possible trigger of cardiac events. Mental stress, defined as a negative state of affect dependent on interpretation or appraisal of threat, harm, or demand (Lazarus, 1966) is generally accompanied by autonomic arousal, resulting in increased release of glucose into the bloodstream, increased cellular metabolism, and redirection of blood flow from the gastrointestinal tract and kidneys to skeletal muscle (Guyton, 1991). Stress has further been associated with a number of physiological processes that may affect the development or progression of coronary disease, including hemodynamic, endocrine, and immunologic changes. Stress causes the release of catecholamines and corticosteroids, as well as increases in heart rate, heart contractility, blood pressure, and cardiac output, and decreases in parasympathetic tone (e.g., Krantz & Manuck, 1984; Pagani, Mazzuero, Ferrari, Liberati, & Cerutti, 1991). Stress may also result in changes affecting the blood clotting process, such as coronary vasoconstriction, platelet aggregation, increased blood viscosity, or plaque rupture (e.g., Muller, et al., 1989; Patterson, et al., 1995; Muldoon, Herbert, Patterson, Kameneva, Raible & Manuck, 1995). These physiological changes may increase the incidence of coronary symptoms or adverse outcomes in patients with coronary artery disease. Stress-related changes may also contribute to the risk of adverse outcomes and clinical events by promoting the

development of atherosclerosis, causing endothelial dysfunction within coronary arteries, triggering arrhythmias, or affecting metabolic risk factors, such as insulin resistance (e.g., Muller, et al., 1989; Kamarck & Jennings, 1991; McEwen, 1998).

Among the earliest studies of psychological triggers of cardiac events are observational studies that reported increases in cardiovascular mortality among individuals who have experienced a recent loss, such as the death of a spouse (e.g., Myers & Dewar, 1975; Cottington, 1980). The validity of these data required further confirmation, however, due to potentially biased recall of stressful events by friends and relatives of the deceased. Ecological studies yielded similar findings. For example, cardiac mortality often increases in the wake of natural disasters, such as earthquakes (e.g., Leor, et al., 1996). Similarly, there was a significant increase in fatal and nonfatal coronary events in Tel Aviv during the Iraqi missile attacks on Israel during the Gulf War (Meisel, et al., 1991).

Acute mental stress in the laboratory. Laboratory data confirm that acute stress can trigger manifestations of cardiovascular disease, such as myocardial ischemia, in many individuals with coronary artery disease (e.g., Gottdiener, et al., 1994; Blumenthal, et al., 1995 Goldberg, et al., 1996). Myocardial ischemia is the result of inadequate myocardial oxygen supply in relation to the demand being placed on the heart and involves inadequate perfusion of cardiac tissue, anaerobic metabolism, diminished or abnormal left ventricular contraction, and electrophysiological changes. Ischemia may also cause chest pain (Rozanski & Berman, 1987). The presence of ischemia is associated with increased risk of adverse cardiac events, independent of coronary anatomy and left ventricular impairment (e.g., Weiner, Ryan, McCabe, Chaitman, Sheffield, et al., 1984).

In the 1970s, it was determined that myocardial ischemia during daily life occurred during periods of little to no physical activity as much as 70% of the time (e. g., Schang & Pepine, 1977). Recently, laboratory studies utilizing sensitive noninvasive means of measuring ischemia, such as radionuclide ventriculography, positron emission tomography, continuous monitoring of left ventricular function, and two-dimensional echocardiography, have revealed that mental stress can trigger ischemia in a substantial subset of CAD patients (Krantz, Kop, Santiago, & Gottdiener, 1996). For example, Deanfield and colleagues (1984) used positron emission tomography to measure myocardial perfusion in 16 patients with coronary artery disease. These patients performed a mental arithmetic task designed to induce stress while regional myocardial perfusion and ischemia were assessed. Twelve patients (75%) had perfusion abnormalities during mental stress. Similarly, in a study conducted by Rozanski and colleagues, CAD patients underwent a series of mental stress tasks while radionuclide ventriculography was used to evaluate left ventricular wall motion and ejection fraction. Among those patients who became ischemic during exercise, 72% showed wall motion abnormalities in response to mental stress. In a large proportion of patients with mental-stress induced ischemia, left ventricular dysfunction during mental stress was severe, with a decrease in ejection fraction of 6% or greater. In several of these patients, the perfusion abnormalities induced by a speech task were similar in magnitude to those induced by physical exercise (Rozanski, Bairey, Krantz, et al., 1988).

It should be noted that mental stress-induced ischemia typically occurs in patients in whom ischemia is also inducible via physical exercise (Krantz, Kop, Santiago & Gottdiener, 1996). Further, stress-induced ischemia often manifests at lesser heart rates and double product calculations compared to exercise, but it is often associated with blood pressure elevations

comparable to exercise. It usually occurs in the absence of chest pain and may not cause discernable electrocardiographic abnormalities (Krantz, Kop, Santiago, & Gottdiener, 1996).

Prognostic value of mental stress-induced ischemia. Myocardial ischemia induced by mental stress has prognostic value with regard to adverse cardiac outcomes, including mortality. In a study of 126 CAD patients with documented exercise-induced ischemia, those patients who experienced ischemia as a result of mental stress were almost three times more likely to die or to have a cardiac event, such as nonfatal infarction, coronary artery bypass graft surgery, or angioplasty, during the 5-year follow-up period than those patients who had no ischemia in response to mental stress. Thus, although mental stress-related ischemia can typically only be induced in patients who become ischemic during exercise, mental stress-induced ischemia carries prognostic value above and beyond that of exercise-induced ischemia. This effect remained even after controlling for traditional risk factors and exercise ischemic response (Jiang, Babyak, Krantz, Waugh, Coleman et al., 1996). Similarly, a follow-up study of 196 CAD patients who underwent mental stress testing as part of the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study revealed that the presence of ischemia in response to mental stress predicts subsequent mortality (Sheps, McMahon, Becker, Carney, Freedland et al., 2002).

Acute mental stress during daily life. It has also been determined that stressful experiences can provoke ischemia in CAD patients during their normal daily activities (e.g., Gabbay, Krantz, Kop, Hedged, Klein et al., 1996; Gullette, Blumenthal, Babyak, Jiang, Waugh et al., 1997). As in laboratory studies of mental stress-induced ischemia, ischemia during daily life most often occurs during sedentary or light physical activity that is associated with relatively

low heart rates. For example, Barry and colleagues utilized a structured diary in which CAD patients recorded their various activities throughout the day. Participants were instructed to make a diary entry whenever their activities changed, to classify each activity as physical or mental, and to classify the intensity of each activity. Initial analysis of the data revealed that most ischemic events occurred during activities described as "usual;" that is, neither restful nor stressful. However, after controlling for the amount of time spent in each type of activity (rest, usual, or stress), analyses revealed a linear relationship between the intensity of activities, both physical and mental, and the likelihood of ischemia (Barry, Selwyn, Nabel, et al., 1988). In a similar study by Gabbay and colleagues, 63 CAD patients underwent ambulatory ECG monitoring (Gabbay, Krantz, Kop, Hedges, Klein, et al., 1996). Using previously validated diaries, patients recorded the start and stop time of their activities, their location, mood, ratings of their control of, involvement in, and expectedness of each activity, and whether or not they experienced chest pain or used nitroglycerin. In these patients, the percentage of time during which ischemia was experienced was greatest during high-intensity activities (5% for both mental and physical activities) compared to periods of time spent in low-intensity activities (0.2%); (Gabbay, Krantz, Kop, Hedges, Klein, et al., 1996). A subsequent study by Gullette and colleagues confirms that high-intensity mental activities increase the risk of ischemia during daily life (Gullette, Blumenthal, Babyak, Jiang, Waugh et al., 1997).

Emotions and the autonomic nervous system. Emotions are defined as complex sets of interactions among subjective and objective factors, mediated by neural and hormonal systems, which can:

1. give rise to affective experiences, such as feelings of arousal, pleasure, and displeasure;
2. generate cognitive processes, such as emotionally relevant perceptual effects, appraisals, and labeling processes;
3. activate widespread physiological adjustments to arousing conditions;
4. and, lead to behavior that is often, but not always, expressive, goal directed, and adaptive (Kleinginna & Kleinginna, 1981).

Emotions are associated with catecholamine release and other autonomic changes, including changes in heart rate, blood pressure, body temperature, and skin conductance (Collet, Vernet-Maury, Delhomme & Dittmar, 1997). Until the early 1990s, emotions were widely assumed to be general, nonspecific states of arousal, with one emotion being physiologically indistinguishable from another (e.g., Schachter & Singer, 1962; Mandler, 1975). However, in response to scattered reports of emotion-specific autonomic activity (e.g., Sternbach, 1962; Roberts & Weerts, 1982), work began in the mid-1980s to determine whether or not individual emotions could be distinguished based on autonomic nervous system parameters, yielding positive results (e.g., Ekman, Levenson & Friesman, 1983).

Generally, six emotions were studied: happiness, fear, surprise, anger, sadness, and disgust. These affective states were defined as basic emotions (Ekman, 1992) because they were assumed to have innate neural substrates (Ekman, Levenson & Friesen, 1983), innate and neural expressions (Bateman & Vanlehn, 1953), and unique feeling-motivational states (Kirouac & Dore, 1983). Although the absolute differences in autonomic responses are not large, it has since been demonstrated that each of these six emotions can be distinguished from one another based on unique, specific autonomic patterns associated with each basic emotion, including hormone

release, heart rate, body temperature, skin conductance, and diastolic blood pressure (Collet, Vernet-Maury, Delhomme & Dittmar, 1997).

Anger and triggering of cardiac events. While most studies of psychological triggers of myocardial infarction and ischemia have focused on the more general concept of stress (i.e., generalized arousal as a result of a perceived threat), several studies have focused on specific emotions as well. Identification of specific emotional responses that increase the risk of adverse cardiac outcomes could shed light on physiologic mechanisms of psychological risk factors and potentially aid in targeting specific behaviors for the purpose of primary and secondary prevention.

Anger, defined as annoyance or antagonism as the result of some real or imagined grievance, is perhaps the most potent and widely studied emotional trigger of cardiac events. By the early 1990s, a number of studies had reported a possible association between emotional and coronary events (e.g., Gelernt & Hochman, 1992; Sumiyoishi, 1986; Tofler, Stone, Maclure, Edelman, Davis, et al., 1990). However, these studies lacked appropriate control data, and therefore could not quantify the association between emotionally stressful events and cardiac outcomes. The case-crossover design provided a methodology with which to collect control data. Mittleman and colleagues interviewed 1623 patients an average of 4 days following their first myocardial infarction. They obtained the time, place, and quality of infarction pain and other symptoms, the estimated usual frequency of anger during the previous year, and the intensity and timing of anger and other potentially triggering factors during the 26 hours prior to infarct onset. The occurrence of anger in the 2 hours preceding infarction was compared with its expected frequency using self-matched control data. These investigators determined that the relative risk

of myocardial infarction in the 2 hours after an angry episode was 2.3 (Mittleman, Maclure, Sherwood, Mulry, Tofler, et al., 1995). The effect of anger was blunted in regular aspirin users, and subsequent analyses revealed that the impact of anger is also moderated by educational level. The risk of experiencing myocardial infarction following an episode of anger was twice as likely among patients with less than a high school education than among those with at least some college (Mittleman, Maclure, Nachnani, Sherwood, & Muller, 1997). It should be noted, however, that these studies rely on self-report of the occurrence, timing, and intensity of anger episodes, and may be subject to recall bias, especially given the potentially traumatic nature of the event that followed.

The strength of the association between anger and cardiac outcome has been bolstered by laboratory and prospective studies, as well. During a laboratory study that evaluated the potency of several psychological stressors and exercise in eliciting myocardial ischemia as measured by left ventricular ejection fraction changes using radionuclide ventriculography, an anger recall speech reduced ejection fraction more than exercise and the other psychological stressors (Ironson, Taylor, Boltwood, Bartzokis, Dennis, et al., 1993). Further, more patients experienced severe reduction in ejection fraction (greater than 7%) during anger than during exercise, suggesting that anger is a particularly potent psychological stressor.

Anger can result in myocardial ischemia during daily life, as well. Using the case-crossover design, Gullette and colleagues (1997) monitored 132 patients with coronary artery disease and documented exercise-induced ischemia on ambulatory ECG monitors for 48 hours. Patients used structured diaries to record their activities and emotions, including frustration, tension, and sadness. Myocardial ischemia was identified using horizontal or downsloping ST-segment depression of 1 millimeter or more for 1 minute or more. Occurrences of negative

emotions in the hour preceding myocardial ischemia were compared with their usual frequency based on all hours in which ischemia did not occur. The relative risk of myocardial ischemia in the hour following high levels of negative emotions was 3.0 for tension, 2.9 for sadness, and 2.6 for frustration. After controlling for concurrent physical activity and time of day, all three risk ratios became 2.2. However, due to a wide confidence interval, the relative risk for sadness no longer reached statistical significance (Gullette, Blumenthal, Babyak, Jiang, Waugh, et al., 1997).

While obviously not an appropriate substitute for human research, animal research has provided possible models for the effects of anger on cardiovascular function. In the late 1980s, Verrier and colleagues developed a canine model to emulate the state of anger. After an overnight fast, each dog is brought into the laboratory and acclimated for 20 to 30 minutes. While secured by a leash, the dog is presented with a bowl of food, which is moved just out of reach. A second dog is the introduced into the room and allowed to consume the food in full view of the first dog. In their laboratory studies, the first dog almost always exhibits an anger-like state in which it growls and exposes its teeth for as long as the second dog is in view. This anger-like state is associated with consistent increases in heart rate, mean arterial blood pressure, coronary blood flow, and plasma catecholamines levels (Verrier, Hagestad, & Lown, 1987; Verrier & Dickerson, 1991).

When subjected to this confrontation model, these dogs experienced profound coronary vasoconstriction 2 to 3 minutes following introduction of the second dog, which persisted well after heart rate and arterial blood pressure recovered. In some animals, blood flow to the heart was sufficiently compromised to induce ischemia (Verrier, Hagestad, & Lown, 1987).

Verrier and Mittleman (1996) suggest that episodes of anger induce the following physiologic characteristics: 1) Rapid-onset tachycardia resulting in impaired diastolic perfusion time leading to ischemia in stenosed coronary circulation; 2) Acute hypertension, resulting in increased cardiac metabolic demand and shear stress with the potential for coronary plaque rupture; 3) Surges in catecholamines (particularly norepinephrine), resulting in predisposition to coronary constriction (especially in the presence of endothelial dysfunction), hightened platelet aggregability, and increased cardiac electrical instability; and 4) Imbalances between coronary hemodynamic and neurohumoral factors, resulting in delayed myocardial ischemia and predisposition to myocardial infarction and arrhythmic death.

Other emotions and triggering of cardiac events. The role of emotions other than anger, such as anxiety and sadness, in triggering cardiovascular events has largely been ignored. Fear, an emotion related to anxiety, has been studied in a somewhat cursory fashion. Studies of natural or man-made disasters, such as the Northridge, California earthquake and the Israeli missile crisis, demonstrate an increase in cardiovascular deaths following events that certainly evoke intense fear (Leor, et al., 1996; Meisel, et al., 1991). An animal model has also been developed for fear-like states. Verrier and Dickerson (1991), using the same food confrontation scenario with dogs described above, note that some animals fail to display anger-like behavior, instead assuming a cowering posture and somatic tremor, which they label a fear-like state. While animals that behave in an angry fashion show increases in plasma norepinephrine, animals that behave in a fearful fashion show increased plasma epinephrine levels. This fear-like state is also associated with increases in heart rate, arterial blood pressure, and coronary arterial flow. Any effects acute fear and anxiety may have on cardiac events in humans can thus far only be inferred

from ecological data, animal models, and the fact that individuals who regularly experience anxiety are at risk for adverse outcomes (see discussion below.)

Data regarding sadness are similarly bereft. There is convincing evidence that individuals experiencing substantial losses, such as that of a spouse, are at increased risk of cardiovascular morbidity and mortality (e.g., Myers & Dewar, 1975; Cottington, 1980). However, these studies have serious limitations due to the risk of recall bias. The only prospective study on the effects of acute sadness is that by Gullette and colleagues discussed above in which sadness was associated with myocardial ischemia until the data were adjusted for time of day and physical activity, at which point sadness failed to reach statistical significance (Gullette, Blumenthal, Babyak, Jiang, Waugh, et al., 1997).

Chronic Environmental Factors

Chronic environmental factors are conditions that may promote coronary disease development or progression and persist over time (Muller, Abela, Nesto et al., 1994). Typically these conditions involve social domains in an individual's life, such as their job, marriage, or family demands. For example, several working conditions that may contribute to coronary disease have been identified, including high psychological demands of the job, low autonomy on the job, and low job satisfaction (e.g., Karasek & Theorell, 1990). Job strain (i.e., the result of high work demands combined with low decision latitude) has been demonstrated to predict cardiovascular disease and mortality in a number of American and European populations (e.g., Karasek & Theorell, 1990; Karasek, et al., 1988; Schnall, et al., 1990). Similarly, family demands have also been associated with incidence of coronary artery disease, especially among

mothers who work outside the home (e.g., LaCroix & Haynes, 1987; Lundberg & Frankenhaeuser, 1999). Low socioeconomic status is also highly associated with cardiovascular disease (e.g., Kunst & Mackenbach, 1994; McDonough, et al., 1997), perhaps due to the chronic stress associated with living within low socioeconomic conditions (e.g., Baum et al., 1999).

The impact of chronic environmental factors is determined, not only by the factors themselves, but also by the resources available for dealing with those factors. For example, social support may mediate the deleterious effects of chronic stress and other environmental factors (e.g., Orth-Gomer & Johnson, 1987). Social support refers to having a variety of social contacts who are available as resources for one's personal benefit (Cohen, et al., 2000). Social support is correlated with a number of health related behavior, such as medical compliance (e.g, Uchino, et al., 1996), but the association between social support and health remains even after statistically controlling for coronary risk factors and risky behaviors (Bland, et al., 1991).

Fitness and usual levels of physical activity. Low levels of usual levels of physical activity (presumably an index of physical fitness) have been associated with cardiovascular morbidity and mortality since as early as the 1950s (e.g, Morris, Heady, Raffle, Roberts, & Parks, 1953). A number of population-based studies have confirmed that higher levels of physical activity decreased an individual's risk of developing or dying from cardiovascular disease. Often, physical activity and levels of fitness were estimated using occupational physical requirements. For example, Taylor and colleagues (1962) followed 191,609 Caucasian male railroad employees aged 40-64 years at baseline for 136,109 man-years. Physical activity levels were estimated using job titles. Participants were placed into one of three categories: clerks (lowest physical activity), section men, and switchmen (highest levels of physical activity).

Atherosclerotic deaths during follow-up were identified using International Classification of Diseases (ICD) codes. Analyses revealed an inverse association between physical activity and atherosclerotic death. The relative risk of cardiovascular mortality was 2.03 for clerks and 1.46 for section men compared to switchmen.

Population studies in which participants were individually asked to report on their levels of physical activity yield similar results. Sesso and colleagues (1999) followed 1564 college alumnae (mean age = 45.5 years at baseline) for an average of 22.4 years. A physical activity index was developed using self-reports of stairs climbed, city blocks walked, and sports played each week. Participants were divided into three categories based on levels of physical activity (< 500 calories expended per week, 500-1000 calories expended per week, and > 1000 calories expended per week), and analyses revealed an inverse relationship between usual levels of physical activity and cardiovascular death. Numerous other population-based studies have yielded similar results (e.g., Paffenbarger, Hyde, Wing & Steinmetz, 1984; Morris, Heady, Raffle, Roberts, & Parks, 1990).

Studies of physical fitness and cardiovascular disease have been conducted primarily on men, perhaps due to higher incidence of cardiovascular disease among men. However, at least one study revealed the same effect in women. A study of 84,129 female nurses investigated physical activity as determined by self-report of time usually spent in moderate to vigorous physical activity (Stampfer, Hu, Manson, Rimm & Willett, 2000). Usual levels of physical activity were inversely related to fatal and nonfatal coronary events during the 14-year follow-up. A recent meta-analysis of physical activity-related research determined that epidemiological data suggest a dose-response effect for exercise and risk of cardiovascular mortality, with more exercise associated with lesser risk (Kohl, 2001). A comprehensive review of the available

literature regarding physical activity and health conducted by the United States Department of Health and Human Services reports that most studies yield an inverse dose-response gradient between level of physical activity and risk of CAD, independent of risk factors such as serum cholesterol, body mass index, blood pressure, and diabetes (USDHHS, 1996).

Physical fitness is also an important predictor of mortality among patients who have already manifested coronary disease. Myers and colleagues (2002) followed 3,679 men with CAD for a mean of 6.2 years and determined that, after adjusting for age, peak exercise capacity was the most powerful predictor of mortality among their independent variables, followed by history of congestive heart failure, history of MI, pack-years of cigarette smoking, left ventricular hypertrophy, pulmonary disease, and exercise-induced ST-segment depression. The American College of Sports Medicine (1994) currently recommends the following exercise guidelines for cardiac patients:

1. Large muscle group, continuous exercise, such as walking, jogging, bicycling, swimming, dance aerobic, and rowing. Strength training may also be appropriate in select patients
2. Minimum frequency of three, nonconsecutive days of the week
3. Warm-up and cool-down periods of at least 10 minutes, including stretching and flexibility exercises and 20-40 minutes of aerobic exercise performed continuously or through interval training
4. Exercise in supervised programs performed at moderate, comfortable intensity (40-85% of maximum heart rate) below a level that provokes ischemia, significant arrhythmia, or symptoms of exercise intolerance. Higher risk patients, such as those with severely depressed left ventricular function,

ventricular arrhythmias appearing or increasing with exercise, and survivors of sudden cardiac death, should exercise at lower intensities.

5. Exercise program should involve an initial slow, gradual progression of exercise duration and intensity.

Hostility and coronary heart disease. A number of longstanding psychological characteristics have been associated with the development and progression of coronary artery disease. Hostility is one such psychological variable that may contribute to variance in cardiovascular events among persons with the same cardiovascular risk factors. Hostility has been described as a mixture of anger and disgust and is associated with emotions such as resentment, indignation, and contempt (Diamond, 1982). It is often accompanied by anger and may carry with it an element of destructiveness. Hostility has been identified as a risk factor for the development of coronary artery disease in a number of studies (e.g., Barefoot, Dahlstron, & Williams, 1983; Shekelle, Gale, Ostfeld, & Paul, 1983). It has also been implicated with regard to the progression of coronary disease and clinical outcomes. For example, hostility has been associated with restenosis following coronary angioplasty and progression of carotid atherosclerosis (Rozanski, et al., 1999).

It should be noted that not all studies of hostility yield positive findings. Although there is a substantial body of literature documenting the effects of hostility (Siegler, 1994), recent meta-analyses have reported that as many as half of the studies of hostility and cardiovascular disease reported null findings (e.g., Miller, et al., 1996; Hemingway & Marmot, 1999). The reasons for these discrepancies are not yet clear, but it may be that hostility is not a risk factor in all populations. It may also be that hostility is difficult to identify, and that the use of different

psychometric instruments by different laboratories may contribute to a lack of homogeneity among published studies of hostility and cardiovascular disease.

Anxiety and coronary heart disease. Another personality trait that may play a role in the development and progression of coronary disease is trait anxiety. Anxiety has been defined as a future-oriented negative affective state resulting from perceptions of threat, characterized by perceived inability to predict, control, or obtain desired results in upcoming situations (Barlow, 1988).

The link between anxiety and cardiovascular disease was first explored among individuals with Panic Disorder and other anxiety-related psychopathology. For example, Coryell and colleagues (1982) followed 113 men and women with Panic Disorder for 35 years. For both men and women, the risk of cardiovascular mortality was twice as high as that of the general population. The researchers did not find a similar excess among other psychiatric populations. Subsequently, Coryell, et al. (1986) identified psychiatric inpatients with probable Panic Disorder and compared their mortality rates to those of age- and gender-matched controls in the same state. Patients with probable panic disorder again had twice the expected mortality rates from cardiovascular disease.

A higher risk of coronary disease has been found among individuals with non-pathological levels of anxiety as well. For example, in a large prospective study of 34,000 men who were initially free of disease, those men who scored highest on an index of phobic anxiety (the Crown Crisp index) were 2.2 times more likely to have fatal myocardial infarctions and 7.7 times more likely to experience sudden death compared to men who scored lowest (Kawachi, Colditz, et al., 1994). Similarly, a 32-year follow-up of 2271 men in the Normative Aging Study

yielded similar odds ratios for fatal heart disease and sudden death for those men reporting two or more symptoms of anxiety of the Cornell Medical Index compared to men who reported no symptoms (Kawachi, Sparrow, Vokonas, & Weiss, 1994).

Depression and coronary heart disease. Although more of an episodic condition than a personality trait, depression has also been associated with the development and progression of cardiovascular disease (e.g., Frasure-Smith, Lesperance, Juneau, Talajic & Bourassa, 1999). Current estimates suggest that Major Depressive Disorder affects 16.2% of U.S. adults in their lifetime. Twelve-month prevalence rates are currently 6.6% (Kessler, Berglund, Demler, Jin, Koretz, et al., 2003). In order to be diagnosed with Major Depression, an individual must have abnormally depressed mood and/or loss of all interest and pleasure most of the day, almost every day, for at least 2 weeks. Additional symptoms must also be present, including weight loss or gain, sleep disturbance, activity disturbance, fatigue, guilt, poor concentration, or suicidal ideation. Symptoms must not be the result of physical illness, alcohol, medication, illicit drugs, or normal bereavement (American Psychiatric Association, 1994).

Depression rates are higher among CAD patients than among the general population, especially among post-myocardial infarction patients. As many as 16-23% of cardiac patients have Major Depressive Disorder (e.g., Schliefer, et al, 1989; Frasure-Smith, et al., 1993), and an additional 30% have depressive symptoms (Frasure-Smith, et al., 1995). Depression rates do not appear to increase markedly with severity of cardiovascular disease or increased disability (Carney, et al., 1987; Frasure-Smith, et al., 1995). CAD patients are also more likely to exhibit atypical depressive symptoms than the general psychiatric patients (e.g., Kop & Ader, 2001; Lesperance & Frasure-Smith, 2000). In order to be identified as atypical depression, the DSM-IV

requires the presence of mood reactivity plus at least additional two symptoms, which may include overeating/weight gain, hypersomnia, leaden paralysis, or interpersonal sensitivity (American Psychiatric Association, 1994). However, studies suggest that the presence of vegetative symptoms (hypersomnia and overeating) are sufficient alone to identify atypical depression (Benazzi, 2002). Compared to melancholic depressive symptoms, atypical depressive symptoms are associated with higher rates of disability and restricted activity days, use of mental health care services, suicidal thoughts, and psychiatric comorbidity (Matza, Revicki, Davidson & Stewart, 2003). Atypical depression is also associated with hypocortisolemia rather than increased neuroendocrine activity, as with melancholic symptoms (e.g., Gold, Goodwin & Chrousos, 1988).

Among individuals with coronary disease, studies have consistently shown that Major Depressive Disorder affects morbidity and mortality. Carney and colleagues (1988) demonstrated that patients with cardiovascular disease who met the criteria for Major Depression were 2.5 times more likely to develop a serious cardiac complication over the next 12 months than nondepressed patients. Similarly, in a later study, 222 cardiac patients were followed after their first myocardial infarction. These patients received structured psychiatric evaluations within 15 days of their heart attack and were followed for 18 months. After controlling for other independent risk factors, Major Depressive Disorder was associated with a 3.5-fold risk of mortality. This risk is comparable to other major risk factors for mortality, such as congestive heart failure and left ventricular function (Frasure-Smith, et al., 1993; Frasure-Smith, et al., 1995).

It appears that the risk of cardiovascular disease associated with depression increases in a linear manner (e.g., Anda, et al., 1993; Pratt, et al., 1996) and that depressive symptoms are

sufficient to increase risk in the absence of Major Depression (Anda, et al., 1993). A number of physiological and behavioral mechanisms have been proposed to explain the link between depression and cardiovascular disease. Depressed individuals are more likely to engage in risk-related behaviors, such as cigarette smoking or lack of physical activity (Carney, et al., 1995). However, depression is still associated with poor cardiac outcomes, even after statistically controlling for traditional risk factors and risk-related behaviors (Glassman & Shapiro, 1998).

2. Biobehavioral factors and cardiac arrhythmia

Most studies of biobehavioral triggers of cardiac events have focused on cardiac ischemia. However, patients with CAD are also often at risk for malignant ventricular arrhythmias, which can lead to sudden death (e.g., Hurwitz & Josephson, 1992).

Ventricular arrhythmias are defined as single or repetitive impulses that originate in the lower chambers of the heart. When they occur in individuals with structural damage to their hearts (as in coronary artery disease), these abnormal impulses may lead to adverse outcomes, including mortality (Myerburg, Catellanos, & Huikuri, 2000). Arrhythmias are caused by abnormalities in (1) cardiac impulse initiation, (2) impulse conduction, or a combination of the two.

Cardiac impulse initiation can occur via two mechanisms: automaticity and triggered activity. Normal cardiac impulses arise spontaneously via the sino-atrial (SA) node. Abnormal automaticity refers to spontaneous impulse initiation in cells that are not fully polarized and is enhanced in the presence of catecholamines. Triggered activity occurs when an after-depolarization achieves sufficient amplitude to reach threshold potential. After-depolarizations

are oscillations of membrane potential that occur during or after an action potential and depend on the preceding action potential for initiation. These oscillations are the result of ionic shifts due to ischemia and reperfusion abnormalities, metabolic influences, autonomic activity (particularly that resulting in hemodynamic changes), or pharmacological toxicity. Triggered activity may become iterative and result in sustained triggered arrhythmias (Myerburg, Catellanos & Huikuri, 2000).

Cardiac impulse conduction is disrupted when a cardiac impulse is blocked, rotates around the nonconductive area, and reenters the site of original excitation in repetitive cycles, a phenomenon known as reentry. Reentry may be anatomical or functional. In anatomical reentry, the repetitive rotation occurs around an area of anatomically nonconductive tissue, such as scar tissue from a prior myocardial infarction. Functional reentrant impulses propagate around an area with conduction block unrelated to anatomical characteristics, such as an area of the myocardium with longer refractory periods than the surrounding tissue (Myerburg, Catellanos & Huikuri, 2000). Cardiac impulse initiation and impulse conduction are adversely affected by myocardial ischemia. Life-threatening arrhythmias are therefore common in patients with CAD and a history of myocardial infarction.

There have been a limited number of studies evaluating the role of biobehavioral factors in triggering arrhythmia. Consistent with the literature on chronic and cute psychological risk factors for myocardial ischemia, preliminary evidence suggests that arrhythmic events are subject to environmental triggers as well.

Acute physical activity and triggering of cardiac arrhythmia. The evidence associating acute physical activity with cardiac arrhythmias is largely anecdotal. However, a review of the

literature reveals that exercise may induce cardiovascular arrhythmia and sudden death. For example, when cardiac arrest occurs immediately following exercise testing or immediately subsequent to collapse associated with exertion, it is almost always preceded by ventricular fibrillation and will almost always respond to prompt application of defibrillatory shock (Cobb & Weaver, 1986). These exercise-induced arrests are typically primary arrhythmic events and are not usually associated with myocardial infarction. Estimates suggest that the additional risk of cardiac arrest conferred by vigorous exertion may be as high as 100-fold (Cobb & Weaver, 1986).

A prospective follow-up of 22,071 male physicians with no history of cardiovascular disease found that the relative risk of sudden cardiac death following 30 minutes or more of vigorous exertion (defined as “exercising hard enough to break a sweat”) was 16.9, although the absolute risk of sudden death during any given bout of vigorous exercise was extremely low. The risk was attenuated by habitual vigorous exercise (Albert, Mittlemant, Chae, Lee, Hennekens & Manson, 2000).

An animal model for the effect of exercise on cardiac arrhythmia has been developed in canines. In a study by Schwartz and colleagues (1984), 57 dogs with prior myocardial infarctions (induced one month before) were instrumented and placed through an exercise stress test. During the last minute of exercise, the left circumflex coronary artery was occluded for 2 minutes in order to induce myocardial ischemia. Ventricular fibrillation was observed in 66% of dogs with infarction (and in 40% of dogs with no infarct). The physiology of those dogs that did not experience ventricular fibrillation indicated the presence of active vagal reflexes, suggesting that vagal response may play an important role in the maintenance of cardiac electrical stability during exercise. A subsequent study using dogs under similar conditions determined that 6 weeks

of daily treadmill training increased heart rate variability, a marker of vagal tone, by 74%. Baroreflex sensitivity, an indicator of the ability of the vagus nerve to moderate heart rate reflexively, increased by 69%, and the repetitive extrasystole threshold, a marker or electrical instability, increased by 44%. The incidence of ventricular fibrillation during acute myocardial ischemia decreased by 100%, suggesting that increased physical fitness associated with regular physical exercise may reduce the acute risk associated with vigorous physical activity (Hull, Vanoli, Adamson, Verrier, Foreman, & Schwartz, 1994).

Ectopic beats during exercise may predict mortality even in apparently healthy, asymptomatic individuals. Jouven and colleagues (2000) subjected 6101 asymptomatic men to treadmill exercise testing. They defined frequent PVCs as a run of two or more consecutive premature ventricular beats or a numebr PVCs constituting more than 10% of all ventricular depolarizations observed in that participant at rest. Participants who experienced frequent PVCs during exercise had higher rates of death from all causes and from cardiovascular causes during the 23-year follow-up period compared to individuals who did not experience frequent PVCs. The risk predicted by frequent PVCs was comparable to that predicted by ischemia during exercise (Jouven, Zureik, Desnos, Courbon & Ducimetiere, 2000).

Cardiac electrical abnormalities during exercise in patients with CAD are important, even if they don’t result in malignant arrhythmias. A study of 163 patients with uncomplicated myocardial infarction subjected patients to symptom-limited low-level treadmill exercise testing and 24-hour ambulatory monitoring before they were discharged from the hospital. Patients were then followed for 2 years, and follow-up status was evaluated for recurrent MI, coronary artery bypass grafting, or death. Ventricular ectopy during treadmill testing was the only single treadmill abnormality that predicted subsequent cardiac death. Chest pain, ST-segment

depression, and hypotensive blood pressure responses were not predictive of mortality. The mortality rate of patients with exercise-induced ventricular ectopy was 25%, compared to an 8% mortality rate in patients who did not manifest ventricular ectopy (Henry, Kennedy, & Crawford, 1987).

Acute stress and triggering of cardiac arrhythmias. The idea that acute mental stress may result in cardiac arrhythmia is not new. As early as the 1930s, it had been noted that experimental animals with a nervous pathway from the hypothalamus to the heart were prone to ventricular arrhythmias, including premature beats, tachycardia, and ventricular fibrillation, often resulting in death (Brow, Long & Beattie, 1930). Because the hypothalamus was believed to be the seat of emotions, it seemed reasonable to hypothesize that arrhythmia could be the direct result of emotional distress. This speculation was reinforced by numerous case reports on individuals who experienced arrhythmia during emotional upset. For example, W. Procter Harvey describes a man who was to receive the first human prosthetic heart valve whose normal sinus rhythm would convert to bigeminy each time his pending operation was discussed. He never received the prosthetic valve because he experienced fatal ventricular fibrillation as he was being prepared for surgery (Taggart, Carruthers & Somerville, 1983).

Taggart and colleagues were among the first to attempt to test this hypothesis. These investigators monitored people with normal hearts, as well as those with coronary artery disease, during a number of stressful situations, including driving during heavy traffic, public speaking, and skydiving (Taggart, Gibbons & Somerville, 1969; Taggart, Curruthers & Somerville, 1973; Shane & Slinde, 1968). Ventricular arrhythmia (premature beats and tachycardia) occurred in nearly all of the CAD patients during stressful situations. Further, even those individuals with

presumably normal hearts experienced ventricular ectopy, albeit to a lesser degree, in response to stress.

More recently, it has been demonstrated that the incidence of sudden cardiac death increases in populations who experience life-threatening disasters, such as earthquakes and war (e.g., Meisel, et al, 1991). For example, on January 17, 1994, a violent earthquake occurred near Northridge, California in the very early morning hours. Leor and colleagues reviewed medical information and coroners' reports following that incident to determine the number of deaths from atherosclerotic cardiovascular disease that occurred following the earthquake relative to the average number at other times. The incidence of sudden cardiac death, often caused by cardiac arrhythmia, on the day of the quake was five times higher than the number that would ordinarily be expected. There were no similar increases among deaths from drug use, cancer, or other diseases. It should be noted that there was a proportionate decrease in sudden cardiac deaths in the days following the earthquake, suggesting that the fear triggered by the natural disaster may have simply hastened the deaths of individuals already at risk.

Laboratory studies have demonstrated that mental stress can induce measurable cardiac electrophysiological disturbances in postinfarct patients (e.g., Tavazzi, Zotti, & Rondanelli, 1986). For example, in a study of 19 patients with recent uncomplicated myocardial infarction, programmed ventricular stimulation was performed at rest and during a mental arithmetic task. During mental stress, the mean ventricular refractory period decreased by 8 milliseconds, and seven patients were provoked into ventricular tachycardia during stress compared to two patients at rest (Tavazzi, Zotti, & Rondanelli, 1986). A subsequent study also used noninvasive programmed stimulation in ten patients with internal defibrillators and a history of ventricular tachycardia (Lampert, Jain, Burg, Batsford, & McPherson, 2000). Participants underwent two

mental stress tasks, mental arithmetic and an anger recall speech. During mental stress, ventricular tachycardia was provoked more quickly and was more difficult to terminate, with four patients requiring a defibrillation shock. These increases in arrhythmia appeared with no evidence of ischemia.

Acute psychological stress has also been demonstrated to induce an increase in QT-dispersion in patients with coronary artery disease (James, et al, 2000). Twenty-four patients undergoing elective coronary angiography were subjected to a series of timed cognitive tasks designed to induce psychological stress. Among the study sample, angiography revealed significant coronary artery disease in 17 participants. Those patients with coronary artery disease who reported feeling stressed in response to the cognitive tasks experienced a marked increase in QT-dispersion, compared to participants with normal coronary arteries who also reported feeling stressed but experienced no change in QT-dispersion. There were no differences in QT-dispersion between normal and CAD participants at baseline.

Acute emotions and triggering of cardiac arrhythmias. There is also some evidence that specific emotions may precede arrhythmias. It has been estimated that 12,000 sudden deaths annually are preceded by episodes of anger (Verrier & Mittleman, 1996). Ventricular tachycardia and fibrillation have also been reported in individuals during frightening dreams (Lown, et al, 1976). However, most studies investigating the role of emotional triggers of cardiac arrhythmia are case reports or otherwise descriptive (e.g., Lown, 1987; Reich, et al, 1981; Frasure-Smith, et al, 1995). For example, Reich and colleagues (1981) examined the effects of acute emotions on malignant arrhythmias in vulnerable individuals. A psychological trigger for the arrhythmia was identified in 21% of participants and preceded the onset of arrhythmia by less than one hour in

13%. However, no control data were collected in this study; therefore, no risk ratios could be calculated. Other studies have focused on induction of arrhythmia in the laboratory via emotional arousal (e.g., Tavazzi, et al, 1986; Lampert, et al, 2000). Lampert and colleagues (2002) further reported that acute anger increased the risk of malignant arrhythmia in ICD patients. However, their data were collected retrospectively and may have been subject to recall bias. To date, no study has prospectively examined the role of emotions in arrhythmogenesis during daily life.

Chronic psychological states and cardiac arrhythmias. Similarly, there is some evidence that chronic emotional states may increase the risk of cardiac arrhythmia and sudden cardiac death. Multiple studies have reported that depression increases the risk of sudden cardiac death among patients with coronary artery disease (e.g., Irvine, et al, 1999; Zeigelstein, 2001; Frasure-Smith, et al, 1995). Anxiety has also been linked to fatal cardiac events, and there is some evidence that anxiety causes autonomic changes that have been associated with cardiac arrhythmia (e.g., Kubzansky, et al, 1998; Friedman & Thayer, 1998). Although acute anger has been substantially associated with cardiac arrhythmia, virtually no data have been published regarding hostility and arrhythmic vulnerability.

Mechanisms by which emotions may trigger arrhythmia. There are a number of mechanisms by which emotions may trigger arrhythmia. One such possibility is reduced activation of the vagus; that is, the nerve which slows heart rate. It has been demonstrated in animal studies that stimulation of the vagus nerve is antifibrillatory. Excitation of the vagus significantly increases the ventricular fibrillation threshold, thereby reducing vulnerability to malignant arrhythmia. Vagal stimulation also reduces the incidence of ischemia-induced

spontaneous ventricular fibrillation. It appears that the primary antifibrillatory action of the vagus is the result of antagonism of detrimental effects of sympathetic nervous system activity via presynaptic inhibition of norepinephrine release and activation of muscarinic receptors, which inhibits second-messenger formation by catecholamines (Verrier & Mittleman, 1996).

In humans, there is no direct evidence for an antiarrhythmic effect of vagal activation, but that some of the mechanisms described in animal studies may also operate in humans and can be inferred by studies that assess vagal activity. For example, a decrease in vagal tone or reflex activation of the nerve as assessed by heart rate variability or baroreceptor sensitivity to phenylephrine infusion are both associated with increased mortality and incidence of sudden cardiac death among patients with a prior myocardial infarct. Further investigation is needed, but it is clear that vagus nerve activation can exert significant beneficial effects on heart rhythm (Verrier & Mittleman, 1996).

Heart rate variability. One means by which vagal activity in humans can be assessed is heart rate variability. Heart rate variability refers to fluctuations in the interval between normal heartbeats. These fluctuations are mediated by autonomic inputs to the sinus node, and therefore provide information regarding cardiac autonomic modulation (Stein & Kleiger, 1999). Heart rate variability first became clinically relevant when researchers noted that fetal distress was preceded by alterations in the intervals between normal heartbeats before any appreciable change occurred in the heart rate per se (Hon & Lee, 1965). Interest in heart rate variability increased as scientists discovered that heart rate is also altered by respiration, a phenomenon now known as respiratory sinus arrhythmia (Hirsh & Bishop, 1981). Subsequent research began to reveal that these patterns of fluctuation were associated with clinical outcomes, such as autonomic

neuropathy in diabetic individuals (Ewing, Martin, Young & Clarke, 1985) and mortality in myocardial infarction patients (Wolf, Varigos, Hunt & Sloman, 1978).

Heart rate variability was originally calculated using simple time domain methods. Time domain measures are obtained by simply determining the length of the intervals between successive normal heartbeats (normal-to-normal or NN-interval; Task Force, 1996). Simple time domain variables include the mean NN interval, mean heart rate, and range of NN intervals. Statistical methods can be used to obtain additional time domain measures. The standard deviation of all NN intervals in a given ECG recording (SDNN) reflects all cyclical components responsible for variability during the time of the recording. SDNN is dependent on the length of recording time, and SDNN measures should only be compared when recording duration is held constant (Task Force, 1996). Other commonly used statistical variables include the standard deviation of the average NN intervals calculated over a short period (SDANN), which is an estimate of changes in heart rate due to cycles of longer than 5 minutes, and the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours (the SDNN index), which estimates the variability due to cycles shorter than 5 minutes (Task Force, 1996).
Statistical measures can also be obtained using measures derived from interval differences. These measure short-term variation and estimate the high-frequency component (Task Force, 1996). Measures of interval difference include the square root of the mean squared differences of successive NN intervals (RMSSD), the number of interval differences of successive NN intervals greater than 50 ms (NN50), and the proportion of intervals greater that 50 ms to the total number of NN intervals (pNN50). The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophyiology recommend that time domain HRV analyses

include a measure of overall HRV (SDNN), an estimate of long-term components of HRV (SDANN), and an estimate of short-term components of HRV (RMSSD; Task Force, 1996). In the early 1980s, power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control was introduced (Akselrod, 1981). Power spectral density (PSD) describes how variance (or power) distributes as a function of frequency (Task Force, 1996). These analyses are known as frequency domain methods. Spectral analyses allow for delineation of four spectral components: high frequency (HF), low frequency (LF), very low frequency (VLF), and ultralow frequency (ULF), which can only be obtained from 24-hour recordings. These components can be measured in absolute units (ms^2) or normalized units (Task Force, 1996).

There is substantial evidence that heart rate and rhythm are largely under autonomic control (e.g., Jalife & Michaels, 1994). The parasympathetic nervous system mediates heart rate via acetylcholine released by the vagus, which causes increased potassium conductivity in cell membranes and inhibition of the pacemaker current (e.g., Sakmann, Noma & Trautwein, 1983; DiFrancesco & Tromba, 1988; Task Force, 1996). Under resting conditions, fluctuations in the interval between heartbeats are largely dependent on vagal modulation (Chess, Tam & Calaresu, 1975). Efferent vagal activity is primarily reflected in the high frequency component of heart rate variability (Task Force, 1996). Low-frequency components may reflect sympathetic modulation or a combination of sympathetic and parasympathetic influences and are not yet completely understood.

Reduced heart rate variability has long been associated with increased risk of mortality in adults without cardiovascular disease, even when taken from ECG recordings as short at 10 seconds. For example, in the “Men Born in 1913 Study,” randomly selected men aged 50 at

baseline were followed for 10 years. Among those men, decreased heart rate variability evaluated using a 10-second ECG strip predicted death from ischemic heart disease (Eriksson, et al, 1989). In 1997, the Zutphen study evaluated HRV using 25-30 second strips from men at rest. They determined that the 5-year age adjusted risk of mortality for middle aged men with low HRV was 2.1 (Dekker, et al, 1997). Similarly, the Framingham study reported that heart rate variability extracted from 2-hour ECG recordings remained predictive of outcome 3.5-4 years later in middle-aged and elderly individuals, even after adjusting for known risk factors (Tusji, et al, 1996; Tusji, et al, 1994).

Reduced heart rate variability is even more predictive of adverse outcome in patients who have had a prior myocardial infarction. In 1987, the investigators of the Multicenter Post-Infarction Project (MPIP) reported that reduced HRV measured within 11 days of MI was associated with a risk of mortality 5.3 times higher than those with higher levels of HRV after one year. The association remained even after controlling for other risk factors, including left ventricular ejection fraction (Kleiger, et al, 1987). In 100 sequential patients undergoing elective coronary angiography, lower HRV predicted mortality during the 1-year follow-up regardless of the extent of coronary artery disease (Rich, et al, 1988).

Post-MI patients with low heart rate variability are at particular risk of sudden cardiac death. In a 2.5-year follow-up of 81 post-infarct patients, reduced HRV predicted sudden cardiac death even among patients already at very high risk for sudden death due to low left ventricle ejection fraction and/or frequent ventricular arrhythmias (Lanza, et al, 1999). In a case report, Nakagawa and colleagues (1994) discuss two post-infarct patients who were monitored via ambulatory ECG recorders on three occasions prior to their eventual sudden death. For both patients, HRV was low in the first recording and progressively lower in each subsequent

recording, suggesting that sequential measurement of HRV may yield even more predictive information.

Heart rate variability and biobehavioral factors. Heart rate variability has been associated with biobehavioral factors, as well. For example, reduced heart rate variability has been reported in depressed individuals. Carney and colleagues (1995) monitored 19 CAD patients with either Major or Minor Depression and compared them with nondepressed CAD patients. Heart rate variability was lower in depressed patients compared to nondepressed patients, even after adjusting for relevant risk factors. Another investigation yielded similar results among moderately to severely depressed individuals (Stein, et al, 2000). These results were later confirmed in a much larger study. Three hundred and eighty acute MI patients with comorbid Major Depression and 424 acute MI patients without depression were monitored for 24 hours. Again, heart rate variability was consistently and significantly lower in depressed patients than non-depressed patients, even after controlling for traditional risk factors (Carney, Blumenthal, Stein, Watkins, Catellier et al., 2001).

Similarly, patients with anxiety disorders, such as Panic Disorder, also exhibit chronically reduced HRV (e.g., Kawachi, et al, 1995). Heart rate variability among individuals without psychopathology, but with high levels of trait anxiety, is largely unexplored. In one study, hostility was also associated with reduced HRV in healthy men younger than 40 years (Sloan, et al, 1994).

Reduced heart rate variability has also been reported in healthy individuals who experience acute emotions. For example, anxiety associated with laboratory tasks such as shock-threat and fear imagery are associated with decreased vagal tone. Anger-inducing laboratory tasks yield a

similar effect (Grossman, et al, 1990). The effects of stress during daily life on heart rate variability have been reported as well. For example, Sloan and colleagues studied changes in heart rate variability using ambulatory ECG monitors (Sloan, Shapiro, Bagiella, Boni, Paik et al., 1994). Thirty-three healthy volunteers were monitored for 24 hours, during which they made diary entries regarding their activities and emotions every hour as prompted by a pager. The investigators combined all reports of negative affect to create an index of stress. During stressful periods, high frequency power was significantly lower, and the high frequency/low frequency ratio was higher, suggesting increases in the relative predominance of sympathetic nervous system activity during stress. A similar study also determined that among healthy, physically fit, and mentally well individuals, elevated perceptions of emotional stress during daily life are associated with depressed vagal tone (Dishman, et al, 2000). However, little has been done to examine the effects of specific emotions on heart rate variability during daily life, particularly in patients vulnerable to malignant arrhythmia.

3. Ecological Momentary Assessment

Ecological momentary assessment (EMA), also known as the experience sampling method (Csikzentmihalyi & Larsen, 1987), is the process of collecting repeated measurements of phenomena as the occur in naturalistic settings (Stone & Shiffman, 1994). It involves signaling participants at predetermined or random intervals throughout the day to report of their immediate experience or current setting, to take physiological readings, or to collect biological samples (Schwartz & Stone, 1998). Typically, studies that utilize EMA involve several prompts per day over one or more days.

This methodology allows for acquisition of more complete information when cognitions, behaviors, or physiological measures are taken on multiple occasions within the context of people's daily routines compared to measurements taken in the laboratory (Schwartz & Stone, 1998). Ecological assessments may more accurately represent the average level and typical variability of a given variable that people experience in their daily lives. Recall bias, which may be associated with retrospective assessment, can be avoided, and psychosocial processes can be investigated in more detail with EMA (Devries, 1987; Schwartz & Stone, 1998). Ecological momentary assessment has been used successfully in the past to measure psychological and behavioral predictors of cardiovascular events (e.g., Gullette, Blumenthal, Babyak, Jiang, Waugh, et al. 1997; Gabbay, Krantz, Kop, Hedges, Klein, et al. 1996).

4. The case-crossover design for the investigation of behavioral cardiovascular risk factors

Historically, it has been difficult to examine the role of triggers of cardiac events using traditional epidemiologic methods due to the risk of selection bias. The case-control method requires selection of controls who adequately represent the case population in characteristics other than the relevant exposure. Unbiased selection of controls is particularly difficult for cardiac patients in that controls must either be healthy, making them fundamentally different from individuals with cardiovascular disease, or they must have a health difficulty other than cardiovascular disease, again introducing potentially confounding variables. In a study of circadian influences on cardiac events, Maclure encountered this obstacle (Maclure, 1991).

Ultimately, he sought to answer the question, “Who would best represent the case population?” Since these investigators were interested in myocardial infarctions that occurred during the morning hours, they considered using CAD patients who had infarcts during the afternoon hours as controls. This reasoning ultimately led them to the possibility of using control time rather than control persons; that is, comparing exposure prior to infarct to exposure at the same time of day on the previous day. This concept yielded perfectly matching controls for each patient: the same patient at the same time on the day before the infarct. Thus, the case-crossover design was developed (Maclure, 1991).

The term “crossover” is typically used to describe experiments in which all participants go through both treatment and placebo phases, “crossing over” between conditions. In the case-crossover design, participants cross over between periods of exposure and nonexposure. It is methodologically appropriate for exposure to risk factors with transient effects because the design requires that subjects cross back and forth between different periods of risk. The case-crossover design utilizes a limited follow-up period, and the control data have units of person-time. Therefore, the parameter estimated in the analysis of case-crossover data is the average incidence rate ratio. Data from each subject are treated as if they were from a matched pair. Rate ratios are estimated using methods appropriate for sparse follow-up data (Maclure, 1991; Maclure & Mittleman, 2000). Specifically, the Mantel Haenszel estimator of the rate ratio and an estimator of the variance of its logarithm are unbiased for sparse person-time data (Greenland & Robins, 1985). Maclure and Mittleman (2000) recommend using Mantel-Haenszel estimates with confidence intervals for sparse data, computed by using formula 12-8 in the first edition of *Modern Epidemiology* (Rothman, 1986), and using conditional logistical regression (Mittleman, Maclure & Robins, 1995).

Since its development, the case-crossover design has been successfully used to evaluate a number of outcomes with transient risk factors, including injuries (e.g., Petridou, Mittleman, Trohanis, Dessypris, Karpathios, et al., 1998), adverse drug events (e.g., Anderson, Gaist, Hallas, & Maclure, 1998), and automobile accidents associated with telephone usage (e.g., Maclure & Mittleman, 1997). It has also been used to examine several transient risk factors for cardiac events, including episodes of physical exertion (Mittleman, Mintzer, Maclure, Tofler, Sherwood, et al., 1993), anger (Mittleman, Maclure, Sherwood, Mulry, Tofler et al., 1995), sexual activity (Muller, Mittleman, Maclure, Sherwood, & Tofler, 1996), cocaine use (Mittleman, Mintzer, Maclure, Tofler, Sherwood, et al., 1999), bereavement (Mittleman, Maclure, Sherwood, Kondo, Tofler, et al, 1996), and respiratory infection (Meier, Jick, Derby, Vasilakis, & Jick, 1998).

Any given risk factor may have both transient and long-standing effects, and the case-crossover design is useful for teasing the two apart. For example, acute physical exertion increases the risk of myocardial infarction immediately subsequent to initiation of activity (Mittleman, Mintzer, Maclure, Tofler, Sherwood, et al., 1996). However, each acute episode contributes in some small amount to increased physical fitness, which reduces the risk of future MI. The case-crossover design allows for each patient's physical fitness to be perfectly matched during periods of exposure and nonexposure to the relevant risk factor (acute physical activity) because each patient is matched to himself. The same principle would also operate when the chronic and acute effects of a risk factor are in the same direction rather than the opposite direction.

Maclure and Mittleman (2000) identify three conditions that must be met in order for a case-crossover study to be successful:

1. It must be feasible to recruit patients rapidly enough for them to be able to recall the day and time of their event.
2. Patients must be able to recall their exposures on control days and/or their usual frequency of exposure.
3. Interview data must be able to be translated into case-crossover analyses with sufficient numbers of discordant patients.

Maclure (1991) further identifies five potential threats to validity in crossover studies: 1) carryover and period effects; 2) treatment sequencing; 3) crossover rules and timing; 4) dropouts and faulty or outlying data; and 5) inappropriate statistical analyses for repeated outcomes. The first threat to validity is relevant in a case-crossover design if there is uncertainty about the duration of the effect period. The second and third are manifest as within-individual confounding because the timing and frequency of crossover are not under the investigator's control. Within-individual confounding may occur if a subject possesses characteristics that change over time. Usually this difficulty can be overcome by additional stratification. Maclure asserts that the fourth threat is manifest as selection or information bias, and that the last does not apply to most cardiovascular outcomes.

Other potential limitations of epidemiologic studies include selection bias, information bias, and generalizability (Maclure, 1991). Selection bias is less of a concern with regard to case-crossover studies because the main source of selection bias, selection of controls who are not representative of the case population, cannot occur. However, case-selection bias is still possible in that some patient's recent exposures may affect their willingness to participate. Information bias continues to be a concern in retrospective case-crossover studies due to potential recall bias. Prospective case-crossover designs eliminate this concern. Typically, the generalizability of a

case-crossover study will be similar to research using other designs and will depend on the same factors.

Summary and Study Rationale

It is important to determine triggers and causes of clinical events in that identification of causes may allow for better prediction of outcomes, elimination of susceptibility, or risk reduction by modification of the cause itself (Maclure & Mittleman, 2000). Although there have been a number of studies examining the effects of psychological factors on myocardial ischemia and infarction, very little is known about these factors with regard to cardiac arrhythmia. The present study seeks to evaluate the role of acute emotions and chronic emotional traits on cardiac arrhythmia during daily life in CAD patients who are prone to arrhythmia. The case-crossover design will allow the acute effects of emotion (e.g., anger) to be examined while controlling for chronic psychological states (e.g., hostility). It will therefore allow for delineation of transient physiological effects of acute emotion separate from the effects of chronic emotional states (to be determined in separate analyses). The present study will also investigate changes in heart rate variability as a result of acute emotions and in individuals with psychological traits, such as depression, and evaluate those changes as a potential mechanism for the effects of emotions on arrhythmia.

Study Aims and Hypotheses

Study Aim 1: To identify proximal triggers of arrhythmia in susceptible individuals during daily life. Using structured diaries and ambulatory electrocardiogram (ECG) data, this

study sought to identify potential triggers of arrhythmia in individuals with internal cardioverter defibrillators (ICDs). Preliminary evidence suggests that behavioral factors, including physical and mental stress, may influence incidence of cardiac arrhythmia in vulnerable individuals (e.g., Willich, et al, 1993; Krantz, et al, 1996; Deedwania & Tofler, 1996). However, the role of external events in triggering cardiac arrhythmia is still poorly understood. The present study examined the role of acute negative emotions and physical activity in triggering arrhythmia in susceptible individuals.

Hypothesis 1a: Acute negative emotions, including anger, sadness, and anxiety, are associated with increased arrhythmia during daily life in vulnerable individuals.

Hypothesis 1b: Acute physical activity is associated with increased arrhythmia during daily life in vulnerable individuals.

Study Aim 2: To identify chronic factors which increase risk of arrhythmia in susceptible individuals during daily life. Using standardized questionnaires and ambulatory ECG data, this study sought to identify chronic factors associated with arrhythmia during daily life in individuals with ICDs. Preliminary evidence suggests that chronic psychological factors, such as depression and chronic anxiety, may increase the risk of cardiac arrhythmia in susceptible individuals (e.g., Dunbar, et al, 1999; Frasure-Smith, et al, 1995). However, most prior research has focused on mortality (i.e., sudden cardiac death). This study examined the role of these chronic factors on arrhythmia during daily life.

Hypothesis 2a: Chronic psychological factors, including hostility, depression, and trait anxiety, are associated with increased arrhythmia during daily life in vulnerable individuals.

Hypothesis 2b: Low levels of usual physical activity will be associated with increased arrhythmia during daily life in vulnerable individuals.

Study Aim 3: To examine heart rate variability as a mechanism by which emotions may trigger cardiac arrhythmias in susceptible individuals during daily life. Using ambulatory ECG data, this study evaluated heart rate variability over 24-hour periods, as well as immediately prior to arrhythmic events in individuals with ICDs. There is considerable evidence the reduced heart rate variability increases the risk of cardiac arrhythmia (e.g., Hohnloser, et al, 1997; Hartikainen, et al, 1996). There is also preliminary evidence that negative emotions may be associated with reduced heart rate variability (e.g., Delaney & Brodie, 2000; Dishman, et al, 2000). However, there is little data regarding changes in heart rate variability throughout the day in response to external events and the impact those changes may have on risk of arrhythmia during daily life.

Hypothesis 3a: Acute negative emotions lead to autonomic shifts which result in reduced heart rate variability.

Hypothesis 3b: Chronic factors, including chronic psychological factors and usual levels of physical activity, lead to autonomic shifts which result in reduced heart rate variability.

Hypothesis 3c: Heart rate variability decreases immediately prior to an arrhythmic event.

Hypothesis 3d: Individuals with lower 24-hour heart rate variability are more prone to arrhythmia.

METHODS

Participants

The present study was conducted on individuals who were previously enrolled in the Triggers of Arrhythmia in Defibrillator Patients (TRIAD) study. TRIAD is an ongoing study that

examines the role of mental stress and other biobehavioral factors in cardiac arrhythmia. In TRIAD, participants underwent a 2-day laboratory protocol, during which the electrophysiology of their heart was monitored during exercise and two mental stress tasks (serial subtraction and an anger recall speech). Subsequent to the laboratory session, participants were fitted with an ambulatory ECG monitor (Holter monitor). They were then monitored for 48 hours during which they also kept structured diaries (described below). Participants also completed several standardized questionnaires.

Participants included 40 men and 10 women with implantable cardioverter defibrillators (ICDs) who were identified from the Cardiology Services of the Washington VA Medical Center, INOVA Fairfax Hospital, and St. Francis Hospital by their cardiologists as part of the TRIAD study. Individuals with programmable ICDs have either had nonfatal cardiac arrest or are at high risk for sudden cardiac death. Device discharges associated with ventricular fibrillation in such individuals could be considered “aborted sudden death episodes. ” Therefore, the occurrence of discharges in these individuals can be used as an outcome variable to test the predictive value of independent variables, such as physical and mental activities, stress reactivity-related changes in heart rate variability, and other physiologically relevant variables for sudden death. Further, these ICDs store ECG data and can be used to identify arrhythmic episodes which do not require a discharge, but are prognostically important (e.g., tachycardia).

To be eligible, participants must have been diagnosed with coronary artery disease and must have received an ICD capable of storing information about each arrhythmia, including time, date, and ECG. Individuals with a primary diagnosis of cardiomyopathy, with severe heart failure, or with neurologic or psychiatric disabilities that would interfere with their ability to understand and respond to mental stress tasks were excluded. Participants were preferentially

recruited if they did not have baseline abnormalities of the ST-segment, and patients expected to undergo coronary revascularization during the period of their involvement in the study were excluded.

Protocol

Medication Titration. Participants who were taking beta-blockers or calcium antagonists who could be safely titrated were tapered gradually from these medications prior to the study. Other anti-arrhythmics, including procainamide, quinine, and digoxin, were continued. Medication titration was authorized by the participant's cardiologist and supervised by a registered nurse. During the ambulatory ECG monitoring period, participants remained off any anti-ischemic medications. Participants were: (1) permitted to take nitroglycerin as needed for chest pain at any time; (2) maintained on isosorbide for 6 hours prior to the study; (3) instructed to resume medications if frequency or severity of angina increased markedly on the regimen; and (4) contacted daily to inquire about their status. The exception to this titration regimen was a minority of participants with demonstrated active ischemia for whom medications could not be ethically withdrawn. Those participants were tested on medications throughout all phases of the study.

Ambulatory ECG monitoring. Immediately after completing the laboratory session, TRIAD participants were fitted with Marquette 3-channel Holter recorders. The method for performing and analyzing ambulatory ECGs has been extensively validated (e.g., Kennedy, 1992). ECG data was collected on cassette tape using a real-time ECG monitoring system.

Recordings were made using a calibrated 3-channel Marquette recorder (frequency 0.05 to 40 Hz). Lead placement was uniform for all participants.

A registered nurse instructed participants with regard to replacing Holter batteries, changing the tapes, re-placing the leads if necessary, and restrictions involved in wearing the Holter (e.g., no showering). Once the participants demonstrated understanding of proper Holter usage, the nurse then instructed them in how to use the structured diaries.

Structured diaries. During the monitoring period, participants completed two structured diaries, one for each day. These diaries were developed in our laboratory and have been validated for use in coronary artery disease patients (e.g., Hedges, et al, 1990). After careful instruction, participants circled activities (physical and/or mental, as appropriate) and rated their moods. Participants were instructed to complete a new diary page whenever activities changed or if their mood changed substantially. Participants were further instructed not to allow time gaps between pages. Participants typically completed about three diary entries per hour. (See appendix for sample diary page and instructions given to participants regarding diaries.) Activities were scored as dichotomous (yes/no) variables, endorsed only if the participant engaged in a particular activity during a given time interval. Rating scales (ranging from 0 to 5) were provided on each diary page for ratings of anger, anxiety, sadness, happiness, involvement, control, expectedness, and levels of mental and physical effort. Participants were specifically instructed to record episodes of anginal chest pain and nitroglycerin use. Diary entries were reviewed for completeness in a face-to-face debriefing session when the diaries were returned. Diary entries were therefore used in order to identify acute periods of sadness, anxiety, and anger. A preliminary examination of the data revealed that increased levels of anger (i.e., any rating

higher than “not at all”) were reported during approximately 17% of diary entries. Anxiety was reported in 22% of entries, and sadness was reported in 7% of diary entries. It should be noted that participants occasionally reported elevated levels of more than one emotion at a time, as negative emotions can be interrelated. For that reason, a composite variable (“negative affect”) was also analyzed (see Gullette, Blumenthal, Babyak, Jiang, Waugh, et al., 1997; Krantz, Kop, Gabbay, Rozanski, Barnard, et al., 1996). Sleep times were excluded from analyses because it was not possible to determine whether patients experience emotions induced by dreaming. As long as sleep is excluded from both case times and control times, this restriction should not result in selection bias.

Standardized questionnaires. Several psychological tests were administered in the TRIAD study. The present study utilized measures of hostility, chronic anxiety, and depression. These measures may reveal individual differences in psychological states and traits that may moderate the presence and/or frequency of arrhythmic events or moderate the arrhythmogenic effects of emotions and activities. Psychometric instruments included:

Beck Depression Inventory - II – The Beck Depression Inventory (BDI; Beck, et al., 1961) is the most widely used measure of depressive severity. A 21-item self-report instrument, each item on the Beck consists of four statements reflecting current manifestations of depression in increasing intensity, from neutral to severe. Scoring of items is on a 0-3 scale, and total scores range from 0 to 63, with higher scores indicating greater depressive severity. Internal consistency for the BDI ranges from .73 to .92, with a mean of .86. Split-half reliability is .93 (Beck, et al, 1988).The Beck also demonstrates acceptable levels of convergent and discriminant validity (Groth-Marnat, 1990). The BDI has subsequently been updated to conform to diagnostic criteria

in the DSM-IV. The revised version (BDI-II) has also been normed on cardiovascular patients (e.g., Beck, Steer & Brown, 1996). Because the BDI-II was self-administered, headings were removed in order to prevent bias due to pre-existing participant expectations and beliefs.

State Trait Anxiety Inventory – The State Trait Anxiety Inventory (STAI; Spielberger, et al, 1970) was designed to measure and differentiate between the temporary condition of state anxiety and the long standing behavior pattern of trait anxiety. The state scale consists of twenty statements that evaluate how the respondent feels "right now," rated on a four-point Likert-type scale from "not at all" to "very much so". The trait scale consists of twenty similarly rated items that assess how the respondent feels "generally." The STAI has been demonstrated to have acceptable content validity and convergent validity (Stanley, et al, 1996; Okun, et al, 1996).

Cook-Medley Hostility Scale – The Cook-Medley Hostility Scale (Cook & Medley, 1954) is a 50-item true/false inventory originally developed from the MMPI. It purports to measure a tendency toward negative emotions, attitudes, and behaviors toward others, and has been demonstrated to have acceptable levels of reliability and convergent and divergent validity (e.g., Smith & Frohm, 1985).

Activities and Mood Questionnaire – Usual levels of physical activity were evaluated using the Activities and Mood Questionnaire (AMQ). Among other lifestyle factors, usual levels of physical activity were rated for frequency using ten intervals ranging from 5 or more times per day to less than once per year or never. Five levels of physical activity were rated on these frequency intervals: Light Activity (light exertion with normal breathing, such as slow walking), Moderate Activity (moderate exertion with deep breathing, such as slow biking), Vigorous Activity (vigorous exertion with panting and overheating, such as slow jogging), Heavy Activity (heavy exertion with gasping and much sweating, such as running), and Extreme Activity

(extreme or peak exertion, such as jogging uphill). For each activity level, participants also reported the specific activity they usually do, the number of times they had done it in the past week, and the duration each time. Participants further reported the number of city blocks they walked each day, their usual pace of walking, and the number of flights of stairs they climbed each day. (See appendix for all psychometric instruments.)

DATA ANALYSIS

1. Power analyses. All power analyses were calculated to determine sample sizes needed for a power > 80% and Type I error (alpha) of < 0.05 using two tailed tests. Specific power calculations are discussed with regard to each hypothesis below.

2. Identification of arrhythmic events. In order to analyze ambulatory ECG data, a Marquette MARS 8000 system was used to digitize the entire ECG tape and extract arrhythmias. The recordings were scanned for ventricular and arrhythmias using computer software with reader validation of ectopic waveforms and sustained arrhythmias. Ventricular beats and runs of ventricular tachycardia were tabulated and quantitatively reported. Ventricular ectopy in the form of accelerated idioventricular rhythm, couplets, triplets, bigeminy, and trigeminy were all considered arrhythmic events, as they are similar in physiologic nature and hold roughly equal predictive value (e.g., Moss, Davis, De Camilla & Bayer, 1979; Ruberman, Weinblatt, Goldberg, Frank & Shapiro, 1977; Ruberman, Weinblatt, Goldberg, Frank, Chaudhary & Shapiro, 1981;

Weaver, Cobb & Hallstron, 1982). Single ventricular beats (PVCs) were also considered in relation to psychological traits, as it has been demonstrated that the presence of ten or more PVCs per hour is predictive of adverse events in individuals with CAD. Further, there is some evidence that three to four PVCs per hour mark the beginning of an increasing risk curve that plateaus at ten PVCs per hour (e.g., Myerburg, Catellanos, & Huikui, 2000).

3. Triggers of arrhythmia. Logistic regression was used to evaluate the role of acute triggers of arrhythmic events. Based on the structured diary, periods of physical activity and periods of negative emotional arousal (i.e., anxiety, anger, and sadness) were identified using a median split of participant ratings of these emotions. It was therefore be possible to identify proximal triggers (physical or mental) of arrhythmias during daily life. Data were analyzed using the case-crossover method, a case-control design that uses each individual as his or her own control, thereby eliminating the need for a healthy control group (Maclure & Mittleman, 2000; Maclure, 1991). Prior studies on the effects of emotions on cardiovascular function suggest that mental arousal affects cardiovascular function for five minutes or less (e.g., Gabbay FH, Krantz DS, Kop WJ, Hedges SM, Klein J, et al., 1996). Therefore, the five-minute period prior to each arrhythmic event was compared to a similar period after which no arrhythmia occurs, yielding rate ratios. Conditional logistic regression with person as the stratifying variable was used to control for multiple arrhythmic events in the same individuals. Because arrhythmias display circadian periodicity (e.g., Peters, McQuillan, & Gold, 1999), the control periods were as close to the same time of day as the case time-period as possible, and “time of day” (morning, afternoon, or evening, depending on clock time) was included in the regression analyses.

The case-crossover design is particularly appropriate for this study in that it increases power by eliminating inter-subject variability. Studies using the case-crossover design are often hampered by recall bias, but this was not a concern in the present study because data collection is prospective, and participants usually will not know when they have experienced an arrhythmia. The case-crossover design will be used only to evaluate the role of biobehavioral triggers of arrhythmia (hypotheses 1a and b). Power analyses based on a prior study of biobehavioral triggers of cardiac events during daily life (Gullette, Blumenthal, Babyak, Jiang, Waugh et al., 1996), assuming that emotions increase the risk of cardiac events twofold and are reported in 12% of diary entries, reveal that at least 241 arrhythmic events are needed for power of .80 with an alpha level of .05. Based on preliminary examination of the data, each subject was expected to have five or more arrhythmic events.

4. Quantification of heart rate variability. Off-line analyses of ECGs were conducted using a Marquette analysis system. In 1996, *Circulation* published a task force committee report containing guidelines for the standardized assessment of heart rate variability and its clinical applications (Task Force, 1996). Heart rate variability analyses can be conducted according to two main strategies: the time domain method and the frequency domain method. In the present study, heart rate variability was analyzed both over long periods of time (24 hours) and short periods of time (immediately preceding an arrhythmic event.) Therefore, both time domain and frequency domain analyses were used.

Time domain analyses were used to examine 24-hour heart rate variability and included: (1) the standard deviation of all NN intervals, which indicates the overall 24-hour heart rate variability; (2) the standard deviation of the average NN intervals calculated over 5-minute

periods; and (3) the square root of the mean squared differences of successive NN intervals (RMSD) as a measure of the short term component of heart rate variability.

In analyses where activities during daily life are cross-tabulated with concomitant heart rate variability components, the frequency domain spectral analysis method was used. These analyses used power spectral density analysis with fast Fourier transformation. Using 5-minute time periods, the minimum amount of time required for frequency domain analyses (Task Force, 1996), three spectral components were identified: very low frequency (VLF; < 0.04 Hz), low frequency (LF; 0.04 Hz – 0.15 Hz), and high frequency (HF; 0.15 Hz – 0.4 Hz).

Given that it is not possible to control fluctuations of heart rate during ambulatory monitoring, possible confounding due to nonstationarity was statistically corrected. Participants with atrial fibrillation were excluded from heart rate variability analyses. Ectopic beats, as well as beats immediately prior and subsequent to ectopic beats, were excluded from heart rate variability analyses. Once triggers of arrhythmia were identified, changes in heart rate variability coincident with and immediately following these triggers were evaluated using regression analysis to determine whether reduced heart rate variability is a mechanism by which physical and mental activities lead to arrhythmic events.

Changes in heart rate variability over time were examined using repeated measures analysis of variance (ANOVA) across all time points with subsequent paired *t*-tests used to compare time intervals only if the repeated measures ANOVAs are significant for changes over time. Assuming a difference of 1 ms^2 and a variance of 1.5 ms^2 based on a prior empirical study of the effects of mental activities on heart rate variability (Kop, Verdino, Gottdiener, O'Leary, Bairey-Merz & Krantz, 2001), power analyses revealed that at least 25 events are needed for

power of .80 with an alpha level of .05. Preliminary examination of the data revealed that most subjects experienced five or more events.

5. Standardized questionnaires. Standardized questionnaires were scored according to their respective manuals, and the impact of these behavioral traits on arrhythmia was evaluated using regression analysis. When data showed evidence of a non-linear effect of a behavioral trait, individuals with “high” verses “low” levels of the trait were identified using a median split, and data were analyzed using two-sample *t*-tests with a Bonferroni corrected alpha of .05. Prior studies of the effects of psychological traits on cardiovascular outcomes suggest that these psychological factors explain a moderate proportion of the variance (e.g., Barefoot, Dahlstrom & Williams, 1983). Therefore in estimating sample size, the effect size was assumed to be medium (.50; Cohen, 1988). Power analyses revealed that 32 participants were required for power of .80 and alpha of .05.

RESULTS

Results are presented in the following order: First, participant characteristics (e.g., demographics, clinical status) and descriptive statistics regarding arrhythmias are presented, followed by individual examination of each hypothesis. Acute triggers of arrhythmia are presented prior to chronic predictors of arrhythmia.

Patient Characteristics

Demographics. Of 50 participants with two 24-hour Holter recordings each, seven participants returned both Holter tapes with no usable data recorded. Eight additional tapes were excluded because they yielded no usable data or contained enough artifact to be considered unreliable, leaving eight participants with only one 24-hour holter recording.

The remaining participants, 39 men and 4 women, had a mean age of 63 +/- 9.5 years, and ranged from 38 to 78 years of age. Eighty-two percent of participants were Caucasian, 10% were African American, 5% were Hispanic, and 3% were Asian. Among female participants, the mean age was 59.5 +/- 14.2 years. Two female participants were Caucasian, one was Hispanic, and one was Asian.

Mean level of education was 15 +/- 3 years, ranging from nine to 20 years. Seventy-eight percent of participants were married, 6% were widowed, 6% were never married, and 10% were separated or divorced. Ninety-two percent of participants lived with at least one other person. Forty-three percent of participants worked full time, while 10% worked part time, 2% were retired, 8% were disabled, and 2% were unemployed. (See Tables 1 and 2 for demographics by gender.)

A group of healthy control participants also enrolled in the TRIAD study (N = 19) were included in some analyses for comparison purposes (e.g., the HRV measures of healthy controls were compared to those of ICD patients for internally validity purposes). Among these healthy controls, 68% were male, and 89% were white. Their average age was 57.79 years (SD = 9.5 years), and they had a mean of 16.89 years of education. Most control participants were married (74%), and 90% lived with at least one other person. Fifty-two percent of controls were current

smokers. Healthy controls did not differ significantly from ICD patients in age ($t = 1.14$, $df = 74$, $p = .26$), but members of the healthy control group were slightly more educated than ICD patients ($t = 2.19$, $df = 65$, $p = .03$). (See Tables 1 and 2.)

Clinical Status, Risk Factors, and Comorbidity. All participants were ambulatory. Seven percent had received an ICD due to resuscitated ventricular tachycardia (VT) or ventricular fibrillation (VF). Twenty-nine percent presented with syncope with VT or VF, 19% with symptomatic VT, 7 % with VT with syncope, 21% with asymptomatic VT, 5% with nonsustained VT, 5% with inducible supraventricular tachycardia, and 7% for wide, complex tachycardia.

Ejection fractions ranged from 20% to 60%, with a mean of 36% +/- 11%. Seventy-four percent had an ejection fraction below 40%, and 33% had an ejection fraction below 30%. Twenty-six percent had a history of cardiomyopathy, 12% had a history of valvular disease, and 7% had left ventricular hypertrophy. Eighty-six percent had at least one prior myocardial infarction, and 42% had a history of multiple infarcts. (See Table 6 for type of infarct.) Forty-seven percent of participants had a history of coronary artery bypass graft surgery, with a mean of three grafts (range = one to five grafts), and half had prior coronary angioplasty. Fifteen percent of participants had one diseased coronary vessel. Twenty-six percent had two diseased vessels, and 30% had three diseased vessels. Thirteen percent of participants had four diseased vessels, and 2% had five diseased vessels. Four percent of participants had a history of atrial fibrillation.

Seventy percent of participants were hypertensive, and 79% were hypercholesterolemic. Twenty-eight percent of participants were diabetic, and 11% were insulin dependent. Fifteen

percent of participants were current smokers, and among the nonsmokers, 84% were former smokers. Those participants who smoked averaged 1.5 packs per day.

Medications and Medication Titration. Before the titration procedure, 81% of participants were on beta-blockers. Nine percent were on calcium channel blockers, 63% were on ACE inhibitors, and 26% used long-acting nitrates. Further, 4% of participants were on amiodarone, 4% were on soltalol, and 9% were on other antiarrhythmic drugs. Participants were only titrated off medications of it could be done safely and with the permission of the patient's physician. Therefore, 26 participants remained on one or more of their medications throughout the study. Sixteen participants continued taking beta-blockers during the study period. One participant continued calcium channel blockers, 13 remained on ACE inhibitors, and 4 continued using long-acting nitrates. For those participants who were titrated off their medications, beta-blockers were withheld for at least 36 hours, calcium channel blockers for 20 hours, ACE inhibitors for 20 hours, and nitrates for 36 hours. No antiarrhythmic drugs were withheld from any participant. (See Table 7.)

Twenty-four Hour Ectopy. The 43 participants with usable Holter data experienced a mean of 2,288 ectopic beats per day, although individual participants varied widely (SD = 3,523; range = 0 - 15,154). Per 24-hour period, participants experienced a mean of 2±5 accelerated idioventricular rhythms, 10± 32 triplets, 124±361 couplets, and 2,003±2851 single ectopic beats. Further, each recording contained a mean of 116±403 episodes of bigeminy and 93±220 episodes of trigeminy. One participant experienced no ectopy during a 24-hour period, and an additional 15 participants experienced fewer than three ventricular beats per hour. No participant

experienced ventricular tachycardia or ventricular fibrillation during the monitoring period. The most severe arrhythmias were accelerated idioventricular rhythms (defined as four or more consecutive ventricular beats at a rate of less than 120 beats per minute), and 21 participants experienced no accelerated idioventricular rhythms during a 24-hour period.

For internal validity purposes, the current sample of participants with ICDs was compared with non-arrhythmia-prone controls with coronary artery disease (CAD controls) and individuals with no heart disease (healthy controls). As expected, compared to healthy controls, ICD patients experienced more total 24-hour ventricular ectopy ($t = 2.24$, df = 45, $p = .04$), more accelerated idioventricular rhythms ($t = 3.03$, df = 45, $p = .004$), more triplets ($t = 2.09$, df = 45, $p = .04$), and more episodes of trigeminy ($t = 2.57$, df = 45, $p = .01$). Differences between ICD patients and healthy controls regarding couplets, single ectopic beats, and bigeminy were marginally significant ($t = 1.88$, df = 45, $p = .07$; $t = 2.13$, df = 45, $p = .054$; and $t = 1.88$, df = 45, $p = .07$, respectively.) Compared to CAD controls, ICD patients experienced more total 24-hour ectopy ($t = 3.63$, df = 67, $p = .001$), accelerated idioventricular rhythms ($t = 2.32$, df = 67, $p = .02$), single ectopic beats ($t = 4.8$, df = 67, $p < .0001$), trigeminy ($t = 2.22$, df = 67, $p = .03$), and maximum number of ectopic beats per hour ($t = 3.8$, df = 67, $p < .001$). Differences between ICD patients and CAD controls regarding triplets, and couplets were marginally significant ($t = 1.8$, df = 67, $p = .08$; $t = 1.7$, df = 67, $p = .09$, respectively.) ICD patients and CAD controls did not differ significantly on episodes of bigeminy ($p = .16$). (See Tables 3-5.)

Proximal Triggers of Arrhythmia

Hypotheses 1a and 1b. Hypothesis 1a predicted that negative emotions and acute would be associated with arrhythmia during normal daily activities. Hypothesis 1b predicted that acute physical activity would also be associated with arrhythmia during normal activities. The relation between exposure to elevated negative emotions and cardiac arrhythmia, and the relation between acute physical activity and cardiac arrhythmia were evaluated using the case-crossover technique comparing the frequency of negative emotions and physical activity during case periods (the hour prior to arrhythmia) to the frequency of emotions and activity during control periods (comparable hours on the alternate day of testing during which no arrhythmia occurred). Because reports of extreme high negative emotion and extreme high physical activity were infrequent, these variables were dichotomized at the median (2 on a scale of 1 to 5) into high and low emotion and high and low physical activity. Conditional logistic regression using the STATA clogit command was conducted with person-hour as the unit of analysis and the participant serving as the stratifying variable (StataCorp, 2003). Each person-hour contained the case-control status, exposure to negative emotions, and physical activity. Because case and control periods were matched for time of day, it was unnecessary to control for circadian variation. Two or more consecutive ventricular beats were considered to be arrhythmic events.

Participants reported feeling frustrated during 17% of case periods, tense during 21% of case periods (periods during which arrhythmic events occurred), sad during 5% of case periods, and stressed during 20% of case periods. More than one negative emotion was reported during 17% of case periods. Participants did not report elevated levels of any individual emotion frequently enough to allow for analysis of each separate emotion, so an aggregate variable of elevated negative emotion was created by combining all reports of frustration, tension, and anxiety rated 2 or higher. Negative emotions were elevated during 46% of case periods.

Participants reported feeling frustrated during 15% of control periods, tense during 20% of control periods, sad during 4% of control periods, and stressed during 19% of control periods. More than one emotion was reported during 15% of control periods. Elevated negative emotions of any kind were reported during 43% of all control periods. Conditional logistic regression analysis revealed an odds ratio for negative emotions of 1.45 (standard error = 0.48, z = 1.15, p = .25), indicating no difference between case and control periods. Results did not change when couplets (the least severe arrhythmia previously included) were excluded.

Unexpectedly, participants reported in engaging in physical activities during 19% of case periods and 32% of control periods. Participants ranked their degree of physical exertion on a scale from one to four, with one being no physical exertion at all and four being a great deal of physical exertion. Participants rated their level of physical exertion as two in 18.70% of case periods and 18.50% of control periods. They rated their level of physical exertion as three in none of the case periods and 13.10% of control periods and as four in 3.70% of case periods and 2.30% of control periods. Mean level of physical exertion was 1.30±0.66 during case periods and 1.52±0.81 during control periods. Conditional logistic regression analysis yielded an odds ratio for physical activity of 0.13 (standard error = 0.07, z = -3.75, p < .0001). Results did not change when couplets were excluded. Regardless of emotion or activity rating, participants reported feeling chest pain and shortness of breath prior to arrhythmic events less than 1% of the time, but they reported feeling significantly more tired prior to arrhythmias compared to control periods (means = 1.78±1.05 and 1.49±0.81, respectively; t = 2.08, df = 102, p = .04).

Because a study published after the collection of the present data reported elevated risk of cardiac arrhythmia following emotional upset in patients with low ejection fractions, additional regression analyses were conducted only on patients with ejection fractions less than 30 (N =

14). Conditional logistic regression analyses of these patients yielded an odds ratio of 1.8 (SE = 1.26, z = 0.94, p = .35). However, when couplets were excluded from the analyses, the odds ratio became 3.67 (SE = 3.22, z = 1.48, p = .14). Results remained nonsignificant due to small sample size and large SE, but *post hoc* power analyses determined that only 57 events would be required for power of .80.

Chronic Factors and Arrhythmia

Hypothesis 2a predicted that psychological factors, including depression, hostility, and trait anxiety, would be associated with increased arrhythmia during normal activities. These chronic factors were first analyzed using zero-order correlations. Due to the two-day monitoring period, some individuals contributed more than 24-hour period of Holter data. However, data were re-analyzed using only the first recording day for each participant, and results remained unchanged.

Depression. Two participants failed to complete the Beck Depression Inventory-II, leaving 48 with this measure. The mean BDI-II score was 6.76± 4.99. Scores ranged from 1 to 23. Women scored significantly higher on the depression inventory than men (t = 2.72, p = .009). Three participants, all men, scored within the mild depressive symptoms range (14-19), and two participants, both women, scored with the moderate depressive symptoms range (20-29). No participants scored in the severe depressive symptoms range (30-63). Unexpectedly, depression was negatively associated with total ventricular ectopy experienced in the 24-hour period (i.e., higher BDI-II scores were associated with lower 24-hour ectopy; r = -.45, p = .02; See Figure 1).

Depression was also negatively associated with episodes of trigeminy (r = -.29, p = .03; See Figure 2), single ectopic beats (r = -.46, p = .02; See Figure 3), the maximum number of ectopic beats experienced in any one hour (r = -.38, p = .004; See Figure 4), couplets (r = -.41, p = .04; See Figure 5), episodes of bigeminy (r = -.39, p = .05; See Figure 6), and accelerated idioventricular rhythms (r = -.45, p = .02). Results remained unchanged when only men were examined. An insufficient number of participants had BDI-II scores above clinical cutoff levels (14 or higher) to analyze them separately. Because cardiac patients are more likely to present with atypical depressive symptoms, vegetative symptoms were analyzed separately. However, there were no significant associations between vegetative symptoms and arrhythmia. Due to the two-day monitoring period, some individuals contributed more than one 24-hour period of Holter data. However, data were re-analyzed using only the first recording day for each participant, and results continued to reveal the same pattern of results.

In order to explore the possibility of a curvilinear relationship between depressive symptoms and arrhythmia, correlations were run separately for patients with ejection fractions greater than and less than 30. These analyses yielded nonsignificant results because of the decreased sample size. However, correlations were remained negative for both groups and were quite large, especially for patients with ejection fractions less than 30 (See Tables 9 and 10 and Figures 9 and 10).

Seven participants failed to complete the Cook-Medley Hostility Scale or completed it incorrectly, leaving 43 with complete scales. The mean score on the Cook-Medley was 16.66±5.72. Scores ranged from 4 to 32. Men did not score significantly higher than women (for men, mean = 16.81±5.82; for women, mean = 15±4.62). Zero-order correlations revealed no significant association between hostility and arrhythmias of any kind, including number of

accelerated idioventricular rhythms (r = -.04, p = .84), episodes of bigeminy (r = -.26, p = .20), couplets (r = -.22, p = .28), single PVCs (r = -.07, p = .73), and total 24-hour ventricular ectopy (r = -.07, p = .72). Results remained unchanged when only men were examined, as well as when participants with very high levels of ectopy were excluded. (See Figures 7 and 8 for representative scatterplots.)

Trait anxiety. The mean trait anxiety score was 6, with a standard deviation of 3. Scores ranged from 2 to 11. Women did not score significantly higher than men (for men, mean = 5.79±2.82; for women, mean = 7.30±4.62). Zero-order correlations revealed no significant association between anxiety and arrhythmias of any kind, including number of accelerated idioventricular rhythms (r = .17, p = .41), episodes of bigeminy (r = -.18, p = .39), couplets (r = .13, p = .54), single PVCs (r = .03, p = .87), and total 24-hour ventricular ectopy (r = .05, p = .82). (See Figures 9 and 10 for representative scatterplots.)

When the Beck Depression Inventory, Cook-Medley Hostility Scale and Taylor Trait Anxiety Scale were entered into regression analyses (first BDI-II, then Taylor, then Cook-Medley), higher BDI-II scores continued to predict fewer accelerated idioventricular rhythms (β = -.59, t = 2.4, p = .03) and couplets (β = -.61, t = 2.6, p = .02). Similarly, higher BDI-II scores were predictive of fewer episodes of bigeminy (β = -.45, t = 1.9, p = .07), single ectopic beats (β = -.46, t = 2.0, p = .06), and total ventricular ectopy (β = -.45, t = 2.0, p = .07). Results remain unchanged when ejection fraction is included in the regression model.

Hypothesis 2b. Hypothesis 2b predicted that low levels of usual physical activity would be associated with increased arrhythmia during a 24-hour period. On average, participants engaged in light activity (defined as light exertion with normal breathing, such as mopping, slow

walking, bowling, gardening with power tools, etc.) five to six times per week and moderate activity (defined as moderate exertion with deep breathing, such as normal walking, golfing on foot, slow biking, raking leaves, etc.) five to six times per week, as well. They engaged in vigorous activity (defined as vigorous exertion with panting, such as tennis, slow jogging, swimming, heavy gardening, etc.) an average of one to three times per month and heavy activity (defined as heavy exertion with gasping and much sweating, such as running, fast jogging, shoveling snow, competitive basketball, etc.) one to three times per year. Participants typically engaged in extreme activity (defined as extreme or peak exertion, such as sprinting, jogging uphill, fast running, etc.) less than once per year or never. These means suggest that participants generally did not exercise as frequently or at the exertion levels recommended by the Surgeon General for patients with cardiovascular disease (USDHHS, 1994). Reported usual levels of light, vigorous, heavy, and extreme physical activity were not associated with any type of arrhythmia. Correlations ranged from .003 to .27; p values range from .16 to .99. (See Table 11 for all correlations.) Participants engaged in heavy and extreme physical activity very rarely, resulting in an inadequate range of scores for those analyses. However, although they were not statistically significant, correlations were in the predicted direction; that is, more frequent heavy and extreme activity were associated with fewer arrhythmias. Surprisingly, more frequent usual levels of moderate activity were associated with more frequent arrhythmias. Moderate activity was positively associated with couplets (r = .45, p = .03) and marginally positively associated with single PVCs (r = .39, p = .06), episodes of bigeminy (r = .39, p = .06), and total 24-hour ventricular ectopy (r = .39, p = .07). There was a similar trend toward a positive association between frequency of moderate activity and accelerated idioventricular rhythms (r = .34, p = .11). (See Figures 11-14.) Ejection fraction was not associated with self-reported usual frequency

of moderate, vigorous, or heavy physical activity. However, patients with lower ejection fractions were more likely to engage in light activity (r = -.37, p = .02), and patients with higher ejection fractions were more likely to engage in extreme physical activity (r = .43, p = .007) and marginally more likely to engage in heavy physical activity (r = .31, p = .055). (See Table 13.) When correlations were repeated controlling for ejection fraction, results did not change substantially. (See Table 12 for correlations.) As a result of the two-day monitoring period, some individuals contributed more than one 24-hour period of Holter data. However, data were re-analyzed using only the first recording day for each participant, and results remained unchanged. When all levels of physical activity were aggregated to form a composite index of usual activity level based on approximate number of calories expended, physical activity was not associated with any type of arrhythmia (rs = -.04 to 0.19, p = .77-.88).

Heart Rate Variability and Acute Emotions

For internal validity purposes, heart rate variability in study participants with ICDs was first compared with that of non-arrhythmia prone participants with coronary artery disease (CAD controls) and participants with no heart disease (healthy controls). In ICD patients, mean SDNN was 114± 43ms. Mean ASDNN was 55± 30ms, mean SDANN5 was 95± 35ms, and mean RMSSD was 38± 46ms. Participants with ICDs had significantly lower SDNN and SDANN5 than CAD controls (t = 2.65,df = 67, p = .01 and t = 2.31, df = 67, p = .02, respectively). ICDs and CAD controls did not differ significantly on SDANN, pNN50, or RMSSD. Because of the small number of healthy controls (7), differences between ICD patients and healthy controls did not reach statistical significance. However, ICD patients did have lower mean HRV than healthy

controls. (Means for healthy controls: ASDNN = 60± 22ms, SDANN5 = 116± 22ms, SDNN = 132± 20ms, pNN50 = 15± 22ms, and RMSSD = 32± 21ms. See above for ICD means. See Table 8 for comparisons.)

Hypothesis 3a. Hypothesis 3a predicted that acute negative emotions would be associated with reduced heart rate variability. Frequency domain measures of HRV were analyzed for the 15 minutes immediately prior to the peak negative emotion recorded in each participant's 24-hour diary. The same measures were recorded in 15-minute intervals at 15, 30, and 45 minutes following the negative emotion. All four 15-minute increments were then compared using repeated measures analysis of variance. Due to the two-day monitoring period, some individuals contributed more than one episode of negative emotion and subsequent HRV measurements. However, data were re-analyzed using only the first episode for each participant, and results remained unchanged.

Prior to negative emotions, mean low frequency HRV was 5.0±1.14 $\ln(ms)^2$. During the 15 minutes immediately following the report of a negative emotion, LF was 5.13±1.13 $\ln(ms)^2$. Thirty and 45 minutes following negative emotion, LF was 4.88±1.29 $\ln(ms)^2$ and 5.01±1.29 $\ln(ms)^2$, respectively. Contrary to the prediction of Hypothesis 3a, low frequency HRV did not change following negative emotions ($F(3, 60) = .42$, p = NS).

Prior to negative emotions, mean high frequency HRV was 4.01±1.20 $\ln(ms)^2$. During the 15 minutes immediately following the report of a negative emotion, HF was 4.07±1.25 $\ln(ms)^2$. Thirty and 45 minutes following negative emotion, HF was 3.95±1.38) $\ln(ms)^2$ and 4.02±1.34 $\ln(ms)^2$, respectively. Contrary to the prediction of Hypothesis 3a, high frequency HRV did not change following negative emotions ($F(3, 60) = .40$, p = NS).

The ratio of low frequency to high frequency HRV was also analyzed as a measure of sympathovagal balance. Prior to negative emotions, the mean LF/HF ratio was 1.31±0.31 $ln(ms)^2$. During the 15 minutes immediately following the report of a negative emotion, LF/HF was 1.56±1.15 $ln(ms)^2$. Thirty and 45 minutes following negative emotion, LF/HF ratio was 1.31±0.30 $ln(ms)^2$ and 1.32±0.29 $ln(ms)^2$, respectively. Contrary to the prediction of Hypothesis 3a, LF/HF ratio did not change following negative emotions ($F(3, 60) = .99$, p = NS). (See Figure 15.)

All ANOVAs were re-run covarying for ejection fraction, but results did not change. *Post hoc* power analyses reveal that samples of nearly 2000 events would be required in order to detect a significant difference in VLF and HF HRV changes. Approximately 400 events would be required to detect statistically significant changes in LF HRV, and over 200 events would be required to detect statistically significant changes in LF/HF ratio.

Because participants reported feeling tired prior to arrhythmias, the associations between reported fatigue and HRV were also explored. However, analyses revealed no significant relationships between reported fatigue and HRV (rs = .03-.22, p = .07-.82).

Heart Rate Variability and Chronic Factors

Hypothesis 3b. Hypothesis 3b predicted that chronic psychological factors, including depression, hostility, and trait anxiety, would be associated with reduced heart rate variability. As predicted, trait anxiety was negatively associated with 24-hour low frequency HRV ($r = -.53$, p = .01) and 24-hour high frequency HRV ($r = -.53$, p = .01), as well as SDNN ($r = -.42$, p = .04) and ASDNN ($r = -.44$, p = .04). (See Figures 16 and 17.) As predicted, the Beck Depression Inventory was significantly and negatively associated with 24-hour high frequency HRV (r = -

.42, p = .04) and marginally associated with 24-hour low frequency HRV (*r* = -.32, p = .12). (See Table 14 and Figure 1.) After controlling for ejection fraction, anxiety scores remained predictive of all of the aforementioned measures of HRV (VLF *r* = -.49, p = .03; HF *r* = -.20, p = .03); SDNN *r* = -.42, p = .04; ASDNN *r* = -.43, p = .04), as well as 24-hour low frequency HRV (*r* = -.65, p = .002). Depression was not significantly associated with any other measure of heart rate variability, including time domain measures, although all trends were negative. Age was associated with BDI-II scores, with younger patients having higher BDI-II scores (r = -.52, p = .001). A partial correlation between BDI-II scores and HF HRV controlling for age yielded marginally significant results (*r* = -.37, p = .09). The correlation between BDI-II scores and LF HRV was rendered nonsignificant by controlling for age (*r* = -.21, p = .34). Anxiety scores were not associated with age (*r* = -.14, p = .26). Neither BDI-II scores nor anxiety scores were associated with ejection fraction (*r* = .10, p = .51 and *r* = .23, p = .12, respectively). Because cardiac patients are more likely to present with atypical depressive symptoms, vegetative symptoms were analyzed separately. However, there were no significant associations between vegetative symptoms and HRV.

Results remained unchanged after controlling for ejection fraction. However, when participants with ejection fractions less than 30 (N = 7) were analyzed separately, associations were even stronger in the predicted direction (*r* = -.57 to -.83, p = .24 to .02; See Table 16 for all correlations). When participants with ejection fractions higher than 30 were analyzed, BDI-II scores were not associated with any measure of HRV (*r* = .07 to -.30, p = .80 to .26). Results regarding anxiety and HRV were unchanged after analyzing participants with ejection fractions higher than 30 and lower than 30 separately.

All correlations between hostility and measures of heart rate variability were negative, but none reached statistical significance. (See Figures 18 and 19 for representative scatterplots.) When depression, anxiety, and hostility (in that order) were entered into regression models, trait anxiety remained a significant predictor of 24-hour low frequency HRV (β = -.69, t = 3.52, p = .004), and was marginally predictive of 24-hour high frequency HRV (β = -.48, t = 4.95, p = .07), low frequency/high frequency ratio (β = -.45, t = 1.81, p = .09), and ASDNN (β = -.48, t = 1.97, p = .07). All of these associations were in the predicted direction; that is, higher anxiety scores were associated with lower HRV.

Hypothesis 3b further predicted that low levels of usual physical activity would also be associated with reduced heart rate variability. Regular vigorous activity was associated with lower average heartrate during the 24-hour period (r = -.36, p = .007). However, usual levels of physical activity were not related to any measure of heart rate variability. Correlations ranged from -.004 to -.35, and p values ranged from .12 to .98. (See Table 13). When all levels of physical activity were aggregated to form a composite physical activity variable, usual levels of physical activity were not significantly related to HRV (r = .14-.42, p = .96-.08).

Because of the two-day monitoring period, some individuals contributed more than one 24-hour period of Holter data. Data were re-analyzed using only the first recording day for each participant, and results continued to suggest that higher anxiety was related to reduced HRV, and usual physical activity was associated with lower 24-hour HRV.

Heart Rate Variability and Arrhythmias

Hypothesis 3c. Hypothesis 3c predicted that heart rate variability would decrease immediately prior to an arrhythmic event. High frequency and low frequency HRV were measured in 15-minute intervals for one hour prior to arrhythmic events. However, when all arrhythmic events, including couplets, were analyzed, no measure of HRV changed prior to arrhythmic events despite the fact that all possible interval comparisons were made (i.e., 60 minutes vs. 45 minutes, 60 minutes vs. 30 minutes, 60 minutes vs. 15 minutes, 45 minutes vs. 30 minutes, 45 minutes vs. 15 minutes, and 30 minutes vs. 15 minutes). Neither did measures of HRV prior to arrhythmic events differ from HRV measures subsequent to arrhythmic events. (See Figure 22.) When couplets were excluded, analyses suggested that low-frequency heart rate variability did change during the hour prior to the arrhythmic event. Means for the 15-minute intervals at 60 minutes, 45 minutes, 30 minutes, and 15 minutes prior to arrhythmic events were 5.85±1.37, 5.59±1.38, 5.79±1.42, and 5.80±1.39, respectively. Repeated measures analysis of variance was marginally significant ($F(3, 120) = 2.36$, $p = .07$). Post-hoc analyses revealed that low-frequency HRV differed most between 60 and 45 minutes prior to arrhythmia ($t = 2.49$, $df = 40$, $p = .017$) and 45 and 30 minutes prior to arrhythmia ($t = 2.32$, $df = 40$, $p = .025$) When only accelerated idioventricular rhythms (the most severe arrhythmia experienced by this sample) were included, low/high frequency ratio increased in the half hour prior to arrhythmia. Means (SD) for the 15-minute intervals at 60 minutes, 45 minutes, 30 minutes, and 15 minutes prior to accelerated idioventricular rhythms were 1.17±0.21, 1.18±0.19, 1.25±0.25, and 1.25±0.28, respectively. Because of the small number of accelerated idioventricular rhythms that occurred, repeated measures analysis of variance did not reach statistical significance ($F(3, 39) = 2.11$, $p = .11$). (See Figure 23.) Due to the two-day monitoring period, some individuals contributed more than one arrhythmic episode and preceding HRV measurements. For that reason, data were re-

analyzed using only the first episode for each participant, and results remained unchanged, indicating no significant changes in HRV prior to ambulatory arrhythmias.

Hypothesis 3d. Hypothesis 3d predicted that individuals with lower 24-hour heart rate variability would be more prone to arrhythmias than individuals with higher 24-hour heart rate variability. However, no measure of 24-hour HRV was associated with arrhythmia (*r*'s range from .01-.24, p = .12-.94; See Table 15 and Figures 24 and 25). Results did not change after controlling for ejection fraction.

DISCUSSION

Summary of Results. The present study sought to identify acute and chronic psychological and behavioral predictors of arrhythmia in patients with internal cardioverter defibrillators. During the two 24-hour monitoring periods, most participants did experience a number of ventricular arrhythmic events, and persons in the study sample experienced more ventricular beats than non-arrhythmia prone controls, with or without coronary artery disease. However, one participant experienced no ectopy during a 24-hour period, and an additional 15 participants experienced fewer than three ventricular beats per hour. No participant experienced ventricular tachycardia or ventricular fibrillation during the monitoring period. The most severe arrhythmias were accelerated idioventricular rhythms, and 21 participants experienced no accelerated idioventricular rhythms during a 24-hour period. Therefore, it should be noted that the findings of the present study apply to less severe arrhythmias, although the arrhythmias examined in this study have been shown to be predictive of malignant arrhythmias (e.g., Myerburg, Catellanos, & Huikui, 2000). Table 17 summarizes hypotheses and obtained study results.

Elevated negative emotions did not increase the risk of cardiac arrhythmias as predicted. Surprisingly, acute physical activity was associated with a reduced risk of cardiac arrhythmia. Hypotheses regarding chronic psychological factors and arrhythmia were not supported. Neither trait anxiety nor hostility was associated with any type of arrhythmia, and surprisingly, higher depressive symptoms were associated with less frequent ectopy. Similarly, most levels of reported physical activity were not associated with any type of arrhythmia. However, reported usual levels of moderate physical activity were associated with more frequent ectopy.

Chronic psychological factors were associated with heart rate variability, as predicted. Both depressive symptoms and levels of trait anxiety were associated with multiple measures of HRV, but hostility was not associated with any type of HRV. Usual levels of physical activity, however, were not associated with HRV.

Hypotheses regarding HRV and arrhythmia were generally not supported. Most measures of HRV were not associated with arrhythmia. However, several measures of HRV were associated with episodes of trigeminy, but not in the predicted direction. Higher levels of HRV were associated with more episodes of trigeminy. Similarly, higher levels of two measures of HRV (SDANN5 and SDNN) were associated with a greater number of ectopic beats experienced in a 24-hour period, as well a higher maximum number of ectopic beats per hour.

When all types of arrhythmia were analyzed, HRV did not appear to change 60, 45, 30, or 15 minutes prior to arrhythmias. However, when couplets (the least severe arrhythmia) were excluded, LF HRV decreased prior to arrhythmic events. When only the most severe type of arrhythmia, accelerated idioventricular rhythms, was analyzed, analyses suggested that LF/HF HRV ratio increased prior to accelerated idioventricular rhythms.

Acute Negative Emotions and Arrhythmia.

In the present study, acute negative emotions were not associated with a significantly increased risk of cardiac arrhythmia. Participants reported negative emotions only 3% more frequently prior to arrhythmias than they did for control periods. Several factors may help to explain the lack of association. The simplest explanation may be that negative emotions within the range experienced by patients in this study are not associated with arrhythmias. Prior studies

that have noted arrhythmias in response to mental stress examined fairly potent stressors, such as skydiving, public speaking, earthquakes, and war (e.g., Taggart, Gibbons & Somerville, 1969; Taggert, Curruthers & Somerville, 1973; Shane & Slinde, 1968; Meisel, et al., 1991). On a scale of one to four, with one being "not at all" and four being "very much", participants rarely rated any negative emotion higher than a two (means ranged from 1.09 to 1.38). It may simply be that participants were not sufficiently stressed in the present study during daily life to trigger an arrhythmia, and that higher levels of mental arousal could trigger arrhythmias. Participants in the present sample also did not experience life-threatening arrhythmias, such as ventricular tachycardia and ventricular fibrillation.

Lampert and colleagues (2002) reported an increased risk of ICD discharge following episodes of acute anger in ICD patients. However, as with the ecological studies and laboratory cited above, the participants in Lampert's study reported much higher levels of emotion than participants in the current study, with their subjects reporting extreme anger (level 5 on a 5-point scale) 8% of the time. Also, the type of arrhythmia required to trigger an ICD discharge is more severe (e.g., VT/VF) than the arrhythmias observed in the current study. The present data do not preclude the possibility that negative emotions may trigger more severe arrhythmias. It is also important to note that participants in the Lampert study did not keep prospective diaries. They were instructed to fill out a diary page only after a defibrillatory shock had occurred and were contacted by the study coordinator within 48 hours of the shock to discuss diary questions and provide guidance if necessary. Control periods were obtained by asking participants to fill out another diary page on the same day of the week at the same time of day as the ICD discharge but one week later. These retrospective data collection techniques may have contributed to recall bias that could potentially bias hypothesis testing toward positive findings. Finally, participants

in the Lampert study appeared to be somewhat less healthy than those in the current study. Twenty-four percent of their subjects received ICDs as a result of sudden death episodes (compared to 7% of the current sample), and 50% presented with sustained VT (compared to 26% of the current sample). It may be that negative emotions predict arrhythmia only in sicker patients.

A study published by Carels and colleagues after the collection of the present data reported an increased risk of arrhythmia following emotional upset, but only in patients with ejection fractions lower than 30 (Carels, Cacciapaglia, Perez-Benitz, Douglass, Christie & O'Brien, 2003). Only one third of the present sample had ejection fractions lower than 30, so separate analyses of that subsample did not yield significant results due to inadequate power. However, the odds ratio for negative emotions was 3.67 in patients with whose ejection fractions were less than 30. Post hoc power analyses revealed that only 57 events would be necessary for power of .80 given this effect size, suggesting that negative emotions do increase the risk of arrhythmia in patients with low ejection fraction. It should be noted that, as in the Lampert study (Lampert, Joska, Burg, Batsford, McPherson & Jain, 2002), participants in the Carels study were in substantially poorer health than those in the current study. In order to meet their inclusion criteria, patients must have had ejection fraction less than 50% and must have been diagnosed with New York Heart Association Class II-IV Congestive Heart Failure. No patients in the present study had a primary diagnosis of congestive heart failure, and there was no restriction on ejection fraction. The discrepancies between these two studies may be explained in large part due to discrepancies in the relative health of the study participants.

Also at issue is the fact that participants made an average of two diary entries per hour, leaving relatively long blocks of time to evaluate. The longest arrhythmic episode experienced

by any participant was an accelerated idioventricular rhythm of 26 beats, which would have lasted approximately 30 seconds. It may be that negative emotions do increase the risk of arrhythmia but that the effects are more transient than those that could be evaluated in the present study. However, participants were instructed to make new diary entries every time their activity and/or mood changed. If participants were exposed to negative emotions prior to arrhythmias, even if they occurred immediately prior to the arrhythmia, those emotions should have at least been recorded in the subsequent diary entry, and they were not, which suggests that negative emotions were not associated with arrhythmias in the present sample.

A similar study examining the role of negative emotions in triggering myocardial ischemia compared exposure to negative emotions during case hours first with time matched control hours, and then with all control hours (i.e., all hours during which no ischemia occurred) in order to increase the power of their study (Gullette, Blumenthal, Babyak, Jiang, Waugh, et al., 1997). The additional control hours brought their relative risk of 2.2 for all emotions to statistical significance. However, such a tactic would not be practical in the present study. The number of control hours used by Gullette and colleagues were simply not available in the present study because of the lack of "clean" control hours in this sample. Participants in this sample experienced mild arrhythmias quite frequently, and there was a dearth of available hours during which arrhythmias did not occur, especially when the hours were matched for time of day.

Acute Physical Activity and Arrhythmia.

Hypothesis 1b predicted that exposure to increased physical activity would increase the risk of arrhythmia. However, conditional logistic regression analysis yielded an odds ratio of

0.38, suggesting that current participants were less likely to have been physically active prior to arrhythmia than during periods when they did not experience arrhythmias. These results were unchanged when patients with ejection fractions less than 30 were analyzed separately. Given prior studies that have demonstrated in the laboratory that acute physical activity increases the risk of arrhythmia (e.g., Cobb & Weaver, 1986), as well as the finding in the present study that participants who usually engaged more frequently in moderate physical activity had more frequent arrhythmias, it seems unlikely that physical activity has a protective effect against arrhythmia. The finding is not confounded by the fact that participants were more active during certain times of the day than others because case periods and control periods were matched for time of day.

It is possible that physical activity has a protective effect on heart rate variability. The effects of acute physical activity on HRV were not evaluated in the present study, so the possibility cannot be eliminated. However, 24-hour HRV was not associated with arrhythmia in the present sample, nor did HRV change significantly prior to the types of arrhythmias most participants experienced in this study. Therefore, it seems unlikely that changes in HRV contributed to the decreased likelihood of arrhythmia after physical activity.

Perhaps the most obvious explanation is that participants didn't feel well prior to arrhythmic events and therefore chose not to be physically active during those times. Participants were not more likely to report chest pain or shortness of breath prior to arrhythmias than at other times, but they were significantly more likely to report feeling tired prior to arrhythmias than during control periods, perhaps making them less likely to engage in physical activity.

Chronic Psychological Factors and Arrhythmia.

Depression. The present data did not support hypothesis 2a. Beck Depression Inventory scores did predict arrhythmias, but not in the predicted direction. All associations between BDI-II scores and arrhythmia were negative. Although no studies to date have examined the effects of depression on ambulatory arrhythmias during daily activities, epidemiological studies have linked Major Depressive Disorder, as well as depressive symptoms, to sudden cardiac deaths, which are generally assumed to be arrhythmic in nature (e.g., Frasure-Smith, Lesperance & Talajic, 1993). In the present study, contrary to *a priori* predictions, higher depressive symptoms were associated with fewer arrhythmias during normal daily activities. Reasons for this disparate finding are unclear, but may include low levels of depression in the present sample, the length of elapsed time since these participants' MIs, and/or the association of depressive symptoms with a protective factor. Each of these possibilities is discussed in detail below.

It should be noted that BDI-II scores in this sample were quite low, resulting in a restricted range of scores for analysis (mean = 6.8, range 1-23). Further, such mild depressive symptoms may not predict arrhythmias, or may not predict them several years after MI. At least one study has demonstrated that depressive symptoms need not meet the criteria for Major Depression in order to increase the risk of mortality in cardiac patients. Bush and colleagues (2001) found that the risk of mortality in post-MI patients with left ventricular ejection fractions of less than 35% was most elevated in those patients who scored higher than 10 on the BDI-II. They also reported that patients with subclinical depressive symptoms (BDI-II scores ranging

from 4 to 9) were at elevated risk of mortality compared to patients scoring less than 4. However, that study evaluated mortality at four months post-MI. Although a large majority of the current study sample has had at least one MI, all but four participants were at least one year post-MI, and most were several years post-MI. It has not been established that the risk of subclinical depressive symptoms extends for years beyond infarct, nor that depressive symptoms specifically predict adverse outcome in ICD patients.

It is possible that the effect of depression on cardiac outcomes is curvilinear. That is, depression may predict adverse outcomes in healthier patients, but not in sicker patients. Prior research has established the increased risk of sudden cardiac death in post-MI patients (e.g., Frasure-Smith, Lesperance & Talajic, 1995). However, participants in the present study have been judged to be sicker than typical post-MI patients in that they are highly prone to malignant arrhythmias and required implantation of a cardioverter device. It has not been established that depression increases the risk of arrhythmias in these sicker patients. However, since the effect of depression on frequency of arrhythmia was not different in patients with ejection fractions greater than 30 than in those with ejection fractions less than 30 in this study, the present data do not support the hypothesis of a curvilinear effect.

Studies of depression in ICD patients have shown that approximately one-third of ICD patients are depressed (e.g., Hegel, Griegel, Black, Goulden & Ozahowski, 1997). One-third of the present study sample scored higher than 10 on the BDI-II, but only 8% scored higher than 16, suggesting that the participants may have been less depressed than the general ICD population. It has been demonstrated that depressive symptoms in ICD patients are associated with the number of shocks the patients receives from the defibrillator (Heller, Ormont, Lidagoster, Sciacca & Steinberg, 1998) and that depressive symptoms in ICD patients decrease over time after

implantation (Dougherty, 1994). Both of these findings may help to explain the low levels of depressive symptoms in the current sample. Because of changing indications for ICD implantation, a large majority of participants in the present sample rarely received defibrillatory shocks. Therefore, most patients in this study were not at increased risk of depression due to frequent shocks. Further, many of them had their devices implanted several years before the study (mean = 4.3 years, SD = 2.3 years, range = 8 months to 12 years), so the average patients may have been beyond the period in which they were most likely to become depressed.

Even given these circumstances, the reason for the positive association (as opposed to no association) is unclear. Participants with BDI-II scores lower than 10 did not include a disproportionate number of women, had no more MIs, and were no less likely to be on beta-blockers or solatol than participants with scores higher than 10. Studies suggest that depressive symptoms increase the risk of mortality in post-MI patients 17%-23% up to 18 months following infarct (e.g., Frasure-Smith, Lesperance & Talajic, 1995; Bush, Ziegelstein, Tayback, Richter, Stevens, et al., 2001). The present study sample, which included many participants who are several years post-infarct, may have resulted in a type of selection bias, in that the patients who live for five or ten years post-infarct without major adverse events may not be at increased risk as a result of depressive symptoms. Without longer prospective studies, it cannot be established that individuals who are at risk due to depressive symptoms experience more adverse events beyond the first year or two post-MI.

Another possible explanation for the negative association between depressive symptoms and arrhythmia in these ICD patients is their unrealistic optimism. Within the context of Taylor's theory of cognitive adaptation, unrealistic optimism has been defined as the illogical belief that one is less likely to experience negative health effects than can realistically be predicted based on

individual risk factors (e.g., Taylor, Kemeny, Reed, Bower & Gruenwald, 2000). This unrealistic optimism, along with other illusions, is believed to buffer against threats and possible setbacks (e.g., Taylor, Kemeny, Reed, Bower & Gruenewald, 2000). People with chronic illness who have lower levels of unrealistic optimism are more likely to suffer psychological distress (e.g., Stiegelis, Hagedoorn, Sanderman, van der Zee, Buunk & van den Bergh, 2003). However, unrealistic optimism is more adaptive in terms of health outcome in illnesses that are not behaviorally managed compared to illnesses that require self-care and behavior modification, including cardiovascular disease (e.g., Fournier, DeRidder & Bensing, 2002).

All the patients in the present sample had been judged by their physicians to be at risk of sudden cardiac death and had serious health problems. The effects of unrealistic optimism were not evaluated in the present study. Still, it is possible that individuals who were realistic about their illness may have manifested more depressive symptoms. At the same time, their realistic appraisals of their conditions may have motivated them toward appropriate behavior modifications that helped to improve their health. Unrealistic optimism was not measured in the present study, so its effects on this sample cannot be determined. However, future studies of unrealistic optimism as a possible protective factor may be warranted.

Trait anxiety and hostility. Neither trait anxiety nor hostility was predictive of arrhythmia during daily activities in this sample. Studies have established that extreme acute anxiety may trigger arrhythmic events (e.g., Taggert, Carruthers & Somerville, 1983), but no studies have linked trait anxiety to increased risk of arrhythmia. The current data do not support the hypothesis that non-pathological levels of trait anxiety increase the risk of arrhythmia in ICD patients. Similarly, hostility did not predict arrhythmia in ICD patients. Studies of hostility and

cardiovascular outcomes have historically been inconsistent and suggest that hostility may only increase risk of some outcomes for certain sub-populations, and that perhaps components of hostility may be more predictive than global hostility scores (e.g., Hemingway & Marmot, 1999; Smith, 1992; Rozanski, Blumenthal & Kaplan, 1999). For example, studies have suggested that the association between hostility and poor cardiovascular outcomes is higher in younger individuals (e.g., Miller, Smith, Tumer, Guijarro & Hallet, 1996) and may be higher in some ethnic groups than others (e.g., Iribarren, Sidney, Bild, Liu, Markovitz, et al., 2000; O'Malley, Jones, Feuerstein & Taylor, 2000). As many as half of all studies of hostility and cardiovascular outcomes report no association (Hemingway & Marmot, 1999). Thus, evidence suggests that hostility is not predictive of ambulatory arrhythmic events in this sample of ICD patients.

Usual Levels of Physical Activity and Arrhythmia. Hypothesis 2b was not supported in that self-reported usual levels of physical activity were generally not associated with arrhythmia. Correlations between usual levels of light, vigorous, heavy, and extreme physical activity and all types of arrhythmia were nonsignificant. Patients in this study rarely engaged in heavy or extreme physical activity, so correlations may have been nonsignificant due to an insufficient range of scores. Those correlations were moderate in size and in the predicted direction; that is, patients who more frequently engaged in heavy and extreme levels of physical activities had fewer arrhythmias. A causal relationship cannot be inferred, however, because healthier patients were far more likely to engage in heavy and extreme physical activity than sicker patients.

More surprising was the fact that more frequent usual levels of moderate activity were associated with more frequent arrhythmias. Epidemiological studies have demonstrated that individuals who regularly engage in higher levels of physical activity are less likely to

experience cardiac morbidity and mortality (e.g., Paffenbarger, Hyde, Wing & Steinmetz, 1984; Morris, Heady, Raffle, Roberts, & Parks, 1990). Though it seems unlikely, it is possible that sicker patients in the present sample were more likely to engage in moderate physical activity than healthier patients. However, ejection fraction was not associated with frequency of moderate physical activity in this sample. This disparate finding could also be due to an effect of physical activity on heart rate variability. However, physical activity was not associated with HRV in this sample, nor was 24-hour HRV associated with arrhythmias in these participants. So, HRV seems an unlikely moderator of this effect.

Perhaps the most obvious explanation for this inconsistency would be that self-report of usual levels of physical activity may not accurately reflect physical fitness. Participants in the present study engaged in physical activity fairly infrequently, with participants reporting engaging in vigorous activity only one to three times per month on average. Light to moderate activity was more frequent, but study measures did not address duration, so the effect of these activities on fitness cannot be conclusively addressed. However, examination of other surrogate measures of physical fitness suggests that these self-report measures do reflect fitness. In the present sample, self-reported frequency of moderate and vigorous activity was negatively associated with body mass index (r = -.448, p = .001 and r = -.278, p = .038, respectively). Further, self-reported frequency of vigorous activity was negatively associated with resting heart rate (r = -.355, p = .007). Thus it appears that regular exercise may not reduce the risk of ambulatory arrhythmias in ICD patients. It may be that these patients had enough structural damage to their hearts that the long-term benefits of improved physical fitness did not override the short term risks of increased physical activity (e.g., Cobb & Weaver, 1986).

These findings are not necessarily inconsistent with prior research in that epidemiological studies have not specifically addressed arrhythmic events, but cardiovascular morbidity and mortality in general. Prior studies were also conducted on individuals initially free of cardiovascular disease. The effects of physical fitness in ICD patients have not been addressed in prospective studies.

Acute Negative Emotions and Heart Rate Variability.

Hypothesis 3a predicted that acute negative emotions would result in decreased heart rate variability immediately following the negative emotion. Analyses did not reveal a significant change in heart rate variability during the 15-minute intervals at 15, 30, and 45 minutes following report of an elevated negative emotion. This finding is in contrast to prior research that has reported decreased vagal tone following anxiety- and anger-inducing tasks in the laboratory (e.g., Grossman, et al., 1990). However, the ecological validity of these laboratory tasks, including the threat of shock and frightening imagery, is unclear. When participants reported negative emotions during daily activities, the causes tended to be fairly benign, such as annoyance with long lines at the bank or telemarketers. Negative emotions reported by participants in this study were of low intensity compared to the emotions evoked in laboratory studies using extreme stressors or by major life events.

It may also be that the participants in the present study had muted or no HRV responses to emotions because their HRV was relatively low at baseline, leaving little room for fluctuation. Although the 24-hour HRV in these ICD patients was not as low as that reported in the literature in other studies of ICD patients, it was significantly lower than that of persons with no coronary

disease, as well as non-arrhythmia prone CAD patients. Participants the aforementioned laboratory studies that showed decreased HRV in response to anxiety and anger were young and healthy, with many studies using college students (e.g., Grossman, et al., 1990). Presumably these healthy participants had higher baseline HRV than individuals with implanatable defibrillators.

Another issue of concern is the timing of diary entries. In a study published after the collection of the present data, Stone and colleagues (2003) placed a light sensor in paper diaries that recorded the dates and times when the diaries were opened. They reported that as many as 80% of entries were made well after the time marked on the diary page, with some entries made on the day following the date of the diary entry. Participants in that study had chronic pain and no heart disease, and the diary protocol was considerably more laborious than that in the present study, but further research using computerized diaries with compliance-promoting features may be warranted in order to confirm the times that entries are actually made. Fluctuations in HRV are highly transient, so even small discrepancies in recording times could obscure an effect.

Chronic Psychological Factors and Heart Rate Variability.

Psychological Factors.

Hypothesis 3b predicted that chronic psychological factors, including depressive symptoms, trait anxiety, and hostility would be associated with reduced heart rate variability in ICD patients. Both depressive symptoms and trait anxiety were associated with lower 24-hour heart rate variability in the present sample. The association between trait anxiety and HRV appears in all patients in this study, but the associations between depressive symptoms and HRV appear to be confined to patients with low ejection fractions.

This finding is consistent with prior studies in which depressed cardiac patients had lower heart rate variability than non-depressed patients. The present finding adds to the existing literature in that the relationship between depressive symptoms and lower heart rate variability has not previously been documented specifically in ICD patients or in patients with reduced left ventricular function. Current findings also demonstrate that sub-clinical depressive symptoms are associated with lower HRV in ICD patients, and that the relationship is linear in nature, becoming stronger with higher depressive symptoms. Specifically, depressive symptoms were associated with lower high-frequency HRV, which is believed to reflect parasympathetic activity, and with lower low-frequency HRV, which is generally believed to reflect both sympathetic and parasympathetic activity, although the specific contributions of each are unclear (Task Force, 1996). It should be noted that HRV typically decreases with age (e.g., Moser, Lehofer, Hoehn-Saric, McLeod, Hildebrandt, & Zapoticzky, 1998). Age was associated with BDI-II scores in the present sample; however, the correlation was negative. The association between depressive symptoms and reduced low-frequency HRV cannot be explained by age, and in fact, the effect may be greater than indicated by the correlation because the younger participants should have higher low-frequency HRV than older patients.

Reduced heart rate variability has been documented in response to acute anxiety in other studies (e.g., Johnson, Thayer, Laberg, Wormnes, Raadal, et al., 2033), but trait anxiety has not previously been associated with HRV. The present study demonstrates that trait anxiety is related to lower heart rate variability in ICD patients. Specifically, trait anxiety was associated with reduced high frequency HRV, low frequency HRV, and 24-hour SDNN and ASDNN. While the implications of low frequency HRV are not clearly understood, high frequency HRV is generally believed to reflect parasympathetic activity (Task Force, 1996). The association between trait

anxiety and SDNN and ASDNN suggest that trait anxiety affects global heart rate variability measures and precludes determination of the specific mechanism involved. The effect further appears to be independent of the association between depression and heart rate variability. Neither were anxiety scores associated with age or ejection fraction.

Although at least one study has suggested that hostility may be associated with reduced heart rate variability in young, healthy men (e.g., Sloan, Bagiella, Shapiro, Kuhl, Chernikhova, et al., 2001), the present study yielded no association between hostility and heart rate variability. These findings are not discrepant in that the present sample was neither young nor healthy, and all participants had ICDs. They are further consistent with the fact that the associations between hostility and cardiovascular outcomes appear to be highly specific (e.g., Hemingway & Marmot, 1999; Smith, 1992; Rozanski, Blumenthal & Kaplan, 1999). For example, studies have suggested that the association between hostility and poor cardiovascular outcomes is higher in younger individuals (e.g., Miller, Smith, Tumer, Guijarro & Hallet, 1996) and may be higher in some ethnic groups than others (e.g., Iribarren, Sidney, Bild, Liu, Markovitz, et al., 2000; O'Malley, Jones, Feuerstein & Taylor, 2000). As many as half of all studies of hostility and cardiovascular outcomes report no association (Hemingway & Marmot, 1999).

Usual Levels of Physical Activity and Heart Rate Variability. Hypothesis 3b further predicted that low levels of physical activity would be associated with reduced heart rate variability. However, in the present sample, self-reported usual levels of physical activity were not associated with heart rate variability. This finding would seem to be in conflict with prior research suggesting that physical fitness is associated with higher heart rate variability (e.g., DeMeersman, 1993). Many of these studies focused on more direct measures of physical fitness, such as exercise testing or measurement of metabolic factors, rather than usual levels of physical

activity (e.g., Rossy & Thayer, 1998). However, higher self-reported usual levels of physical activity are associated with lower body mass index and lower resting heart rate in the present sample, suggesting that they do reflect physical fitness to some degree.

The discrepancy may also be explained by the fact that many studies examining the effects of physical fitness on heart rate variability compare athletes to non-athletes. For example, DeMeersman (1993) suggested that exercise may be a beneficial modulator of heart rate variability, but this conclusion was based on a cross-sectional study comparing habitual runners to sedentary adults.

Heart rate variability may have been attenuated in the current sample because of changes associated with aging. However, it has been demonstrated that individuals who exercise regularly have higher heart rate variability than sedentary individuals, even among older adults (Yataco, Fleisher & Katzel, 1997). Therefore, it seems unlikely that age obfuscated an effect of physical fitness on HRV in the present sample.

Perhaps the most likely explanation for the lack of association between physical activity and heart rate variability in the present study is the fact that participants were largely inactive. Most participants engaged in physical activity fairly infrequently and then at low levels of intensity, with the average participant engaging in vigorous physical activity less than one time per week. A prospective study of patients enrolled in a cardiac rehabilitation program after a cardiac event demonstrated that exercise conditioning significantly increases heart rate variability, but only in participants who increased their activity levels by greater than 1.5 metabolic units (METS) over a 12 week period (Pardo, Merz, Velasquez, Paul-Labrador, Agarwala & Peter, 2000). Based on self-reported activity level, there is no evidence that the majority of patients in the current sample were exercising at a conditioning level.

Heart Rate Variability prior to Arrhythmic Events.

Hypothesis 3c predicted that heart rate variability would change prior to arrhythmic events. When all arrhythmic events, including couplets, triplets, bigeminy, and accelerated idioventricular rhythms were included in analyses, heart rate variability did not change prior to arrhythmias. To rule out the possibility that changes in HRV prior to more severe arrhythmias were being obscured by the inclusion of less severe arrhythmic events, couplets – the most common and least severe type of arrhythmia – were excluded from subsequent analyses. When couplets were excluded, low frequency HRV decreased at 45 minutes prior to the arrhythmia, and rebounded by 15 minutes prior to the arrhythmia. As discussed above, the factors contributing to low frequency HRV are unclear, but it is believed to reflect both sympathetic and parasympathetic influences to some degree (Task Force, 1996). Although high frequency HRV and the low frequency/high frequency ratio did not change to a statistically significant degree prior to arrhythmias, they do show similar trends in their means with a decrease at 45 minutes pre-arrhythmia and rebound by 15 minutes prior to arrhythmia.

When all arrhythmias except accelerated idioventricular rhythms (the most severe arrhythmia experienced by patients in the present sample) were excluded, changes in HRV prior to the event did not reach statistical significance due to inadequate power as a result of the small number of accelerated idioventricular rhythms that occurred in this sample. However, one noteworthy trend emerged: the low frequency/high frequency HRV ratio increased at 30 minutes prior to the accelerated idioventricular rhythm and remained elevated until the idioventricular rhythm occurred. This change indicates a shift away from vagal modulation (reflected in high

frequency HRV) prior to accelerated idioventricular rhythms. Such a shift would be consistent with animal research suggesting that vagal activity has anti-arrhythmic effects (e.g., Verrier, Hagestad, & Lown, 1987; Verrier & Dickerson, 1991), as well as research indicating a shift to sympathetic predominance prior to tachyarrhythmias (e.g., Chiladakis, Pashalis, Patsouras & Manolis, 2001; Lombardi, Porta, Marzegalli, Favale, Santin, et al., 2000).

Twenty-four Hour Heart Rate Variability and Arrhythmia.

Hypothesis 3d predicted that lower levels of heart rate variability would be associated with more frequent arrhythmias during daily activities. However, no measure of heart rate variability was in any way associated with ambulatory arrhythmias in the present sample. This finding is inconsistent with prior studies that found associations between low heart rate variability and subsequent arrhythmic events (e.g., Lanza, Galeazzi, Guido, Luciente, Bellocci, et al., 1999); however, there are several possible explanations for the discrepancy.

First, although participants had been judged by their physicians to be at high risk for ventricular arrhythmias, and although ICD patients had lower heart rate variability than normal individuals or non-arrhythmia prone individuals with coronary artery disease, their heart rate variability was still relatively high. For example, Vaage-Nilsen and colleagues (2001) found that SDNN lower than 30ms during the day and 18 ms during the night predicted 9-year mortality. ICD patients in the present sample had a mean SDNN of 111 ms (SD = 41). They also found that after one year post-MI, SDNN has no prognostic value. As discussed previously, most participants in the present study were several years post-MI.

It may also be that heart rate variability is simply not predictive of arrhythmia in ICD patients. Although HRV predicts mortality from sudden cardiac death in CAD patients (e.g., Lanza, Galeazzi, Guido, Luciente, Bellocci, et al., 1999), HRV may not be predictive of arrhythmia in other cardiac populations, such as patients with dilated cardiomyopathy (e.g., Grimm, Herzum, Muller & Christ, 2003).

Finally, the possibility that beta blockers affected heart rate variability in this sample cannot be eliminated. For example, Acanfora and colleagues (2000) demonstrated in a randomized placebo trial that propanolol increased high frequency HRV and decreased low frequency HRV, thereby decreasing the low frequency/high frequency ratio in coronary artery disease patients with severe ventricular arrhythmias (Acanfora, Pinna, Gheorghiade, Trojano, Furgi, et al., 2000). A large majority of the patients in the present sample had been prescribed beta blockers. Although most of them were titrated off beta blockers before the study began, it is unclear how long the effects of beta blockers on HRV may continue after the drug is discontinued. Controlling for the effects of beta-blockers may not be realistic for most ICD patients as the prescription of beta-blockers is standard treatment in arrhythmia-prone patients (Oseroff, Retyk & Bochoeyer, 2004).

Study Limitations and Future Directions

The present study was limited by the fact that none of the ICD patients experienced severe arrhythmias during the study protocol. The most severe arrhythmias experienced by any participant were accelerated idioventricular rhythms, and most of them were fairly short in duration (mean = 6 beats). Several large, clinical trials have demonstrated that ICDs prolong

life in patients vulnerable to malignant arrhythmias. Therefore, it is reasonable to expect that ICD patients are at high risk for life-threatening arrhythmias. However, current guidelines suggest that ICDs be implanted in patients with fairly severe arrhythmias. For example, the Antiarrhythmics versus Implantable Defibrillators (AVID) study reported a substantial decrease in mortality among patients who had been rescusitated from near-fatal ventricular fibrillation, who had presented with sustained VT with syncope or sustained VT with an ejection fraction less than 40% and symptoms suggesting severe hemodynamic compromise due to arrhythmia, such as near-syncope, congestive heart failure, and angina (Zipes, Wyse, Friedman, Epstein, Hallstrom, et al., 1997). The Multicenter Automatic Defibrillator Implantation Trial (MADIT) study used less stringent inclusion criteria. Nevertheless, the mean ejection fraction among their study sample was still extremely low (25% compared to 37% with a range of 20-60% in the present sample). More recent studies have reported health benefits of ICD implantation that do not necessarily involve prolonged survival in patients with less severe arrhythmias, such as non-sustained VT (e.g., Evonich, Maheshwari, Gardiner, Khasnis, Kantipudi, et al., 2004). These findings promote the implantation of devices in healthier patient populations, including many participants in the current study. It could be argued that the current sample were at lower risk for malignant arrhythmia than those in prior studies.

The increasingly common prophylactic use of internal defibrillator coupled with widespread use of the highly effective antiarrhythmic drug, amiodarone, has led to a large number of ICD patients who rarely experience arrhythmias severe enough to warrant ICD discharge. Because many patients were healthier than patients who have historically received ICDs, they may have had a higher threshold for arrhythmias, making them less sensitive to environmental triggers. Some of the psychological variables in this study, such as depressive

symptoms, may have also been affected by the lack of discharges (e.g., Heller, Ormot, Lidagoster, Sciacca & Steinberg, 1998). It may be beneficial to examine patients with a clear history of arrhythmia post-ICD implant in the future. However, although current guidelines do not address the less severe arrhythmias observed in the present study, prior research has demonstrated that they are predictive for future malignant arrhythmias (e.g., Myerburg, Catellanos & Huikui, 2000). More recent research continues to support these findings. For example, in a prospective follow-up as part of the MADIT II trials, Berkowitsch and colleagues (2004) reported that conventionally (i.e., antiarrhythmic drug) treated patients who had more than 3 PVCs in a 10-minute holter recording were significantly more likely to die during the follow-up period than those who experienced fewer or none. Similarly, ICD patients who had frequent PVCs were more likely to receive appropriate defibrillatory shock therapy than patients who had fewer or none. The less severe arrhythmias observed in the current study remain predictive of morbidity and mortality in patients with structural heart damage.

Another possible limitation of the present study was the fact that so many participants were several years post-MI and had received ICD several years earlier. For example, some studies have suggested that the depressive symptoms decrease over time after ICD implant (e.g., Dougherty, 1994), and it has not been demonstrated that depressive symptoms have detrimental effects beyond 18 moths post-infarct (e.g., Frasure-Smith, Lesperance & Talajic, 1995; Bush, Ziegelstein, Tayback, Richter, Stevens, et al., 2001). In future studies, it may be prudent to examine patients who are less than two years post-infarct and have recently received ICDs.

This study relied heavily upon self-report data (i.e., diary reports and psychosocial tests). While self-report measures have a number of advantages, they are also inherently limited by the possibility of issues such as recall bias and social desirability. Studies published after the

collection of the present data suggest that patient compliance with paper diaries may be low (e.g., Stone, Shiffman, Schwartz, Broderick & Hufford, 2002). In studies of presumably transient effects, determining the precise timing of exposures is important. In future studies, electronic diaries may be useful to increase compliance and more precisely identify environmental triggers of cardiac events. In future studies on the effects of physical activity, it may also be useful to collect more objective measures of physical fitness, such as metabolic variables, aerobic capacity, and cardiovascular endurance, in addition to self-report of usual levels of physical activity.

It should be noted that heart rate per se was not recorded along with the measurements of heart rate variability prior to arrhythmias and subsequent to mental stress. Given the counterintuitive finding of essentially unchanged HRV under both of these circumstances, analysis of heart rate is necessary for comprehensive interpretation of these data and should be included in future analyses.

Finally, the analysis of heart rate variability in the present sample was complicated by the presence of ectopic beats and their exclusion in data analyses. In order to properly analyze HRV, not only must the technician exclude all ectopic beats, but a normal beat both before and after the ectopic beat must also be excluded. The result is the exclusion of a percentage of beats from analyses. Although HRV is a valuable component of risk stratification, in ICD patients, the additional analysis of a variable called heart rate turbulence may provide additional important information. Heart rate turbulence is a new method of risk stratification that has recently been demonstrated to predict sudden cardiac death in post-myocardial infarction patients independent of other known risk factors, including left ventricular ejection fraction and heart rate variability (e.g., Bauer & Schmidt, 2003). The phrase “heart rate turbulence” refers to the fact that low risk

individuals show a characteristic pattern of early acceleration and subsequent deceleration of sinus rhythm following single ectopic beats. Like some measures of HRV, it reflects vagal activity. However, rather than excluding ectopic beats, heart rate turbulence evaluates the short-term fluctuation of the sinus rhythm cycle (normal heartbeats) immediately prior to and following ectopic beats. In post-infarct patients at high risk of sudden death, heart rate turbulence is decreased or absent. Studies suggest that heart rate turbulence may be a useful predictor of mortality even for patients in whom other predictors, such as heart rate variability, are less useful (Bauer & Schmidt, 2003). Because heart rate turbulence evaluates the exact beats that are excluded from HRV analyses, the addition of heart rate turbulence to future studies of biobehavioral triggers of arrhythmia may help to present a more complete analysis of risk.

Summary. In the present study, as predicted, higher levels of trait anxiety and chronic depressive symptoms were associated with lower measures of heart rate variability. Although all associations between hostility and HRV were negative (i.e., higher hostility associated with lower HRV), the associations were small and did not reach statistical significance.

Participants appear to have been more likely to be exposed to acute negative emotions prior to more severe cardiac arrhythmia, such as bigeminy, triplets, and accelerated idioventricular rhythms, compared to control periods when no arrhythmia occurred. This association was not present when couplets were included in the analyses.

In the present sample, HRV did not change significantly prior to arrhythmic events. However, nonsignificant changes were consistently in the predicted direction (decreasing prior to arrhythmias). The changes in HRV prior to more severe arrhythmias, particularly accelerated idioventricular rhythms, were considerably larger than those prior to more benign arrhythmias

(such as couplets), but the small number of more severe arrhythmias experienced by the present sample prevented those changes from reaching statistical significance.

Surprisingly, participants were less likely to have been exposed to acute physical activity prior to arrhythmia than during control periods when no arrhythmia occurred. This finding is likely due to the fact that patients didn't feel well prior to arrhythmias and therefore chose not to be physically active at that time. Although they did not report increased chest pain or shortness of breath prior to arrhythmias, there was no measure of general malaise, and patients were significantly more likely to report feeling tired prior to arrhythmias compared to control periods.

Further, higher depressive symptoms were unexpectedly associated with fewer arrhythmias. This disparate finding may be due to a type of selection bias due to the length of time that had passed since participants had their first infarct and the length of time that had passed since their ICDs were implanted. Given the low levels of depressive symptoms in this sample, this finding may also reflect a maladaptive level of unrealistic optimism. Further study is necessary to determine the role of unrealistic optimism in cardiovascular outcomes. Neither hostility nor trait anxiety was associated with cardiac arrhythmia.

Self-reported usual levels of light, vigorous, heavy, and extreme physical activity were not significantly associated with any type of arrhythmia. However, nonsignificant correlations were all in the predicted direction; that is, more frequent heavy and extreme activity were associated with fewer arrhythmias. Unexpectedly, higher levels of moderate activity were significantly associated with more frequent arrhythmias, which may indicate that the acute risk of physical activity outweighs the benefit of consistent activity. It may also be that participants in the present sample did not exercise frequently enough for physical activity to be beneficial. It is unclear whether self-reported usual levels of physical activity adequately reflect physical fitness

levels. However, correlations between reported activity levels, resting heart rate, and body mass index suggest that they do reflect physical fitness, at least to some extent. Additional research using more objective measures of physical fitness, such as aerobic capacity and cardiovascular endurance, may help to clarify these findings. Usual levels of physical activity were not associated with any measure of heart rate variability.

Contrary to predictions, heart rate variability did not change following negative emotions, perhaps due to low baseline levels of HRV that did not allow for much fluctuation. This finding may help to explain why exposure to acute negative emotions did not increase the risk of arrhythmia.

Measures of 24-hour HRV were not associated with the frequency of arrhythmias in the present sample, which may reflect the lack of an association between HRV and arrhythmia in ICD patients, but may also be the result of lingering effects of beta-blockers.

TABLES AND FIGURES

Table 1. Demographics and Clinical Status: All Participants

Age (mean +/- SD)	63 (+/- 9.5) years
Race	82% Caucasian 10.0% African-American 5.0% Hispanic 3% Asian
Sex	90% Male 10% Female
Ejection Fraction (mean +/- SD)	36 (+/- 11)
History of Myocardial Infarct	86%
Number of Diseased Vessels One Two Three Four Five	 15% 26% 30% 13% 2%
Comorbidity Hypertension Hypercholesterolemia Diabetes	 70% 79% 28% (11% Insulin dependent)
Presenting Arrhythmia Syncope with VT or VF Symptomatic VT VT with syncope Symptomatic VT Nonsustained VT Inducible SVT Wide complex tachycardia	 29% 19% 7% 21% 5% 5% 7%

Table 2. Demographics: Women Only

Age (mean +/- SD)	59.5 (+/- 14.2) years
Race	50.0% Caucasian 25.0% Hispanic 25.0% Asian

Table 3. Ventricular Ectopy: All Participants

Type of Ectopy	Range	Mean	Standard deviation
Total ventricular ectopy (24 hr)	0-15,154 beats	2,288 beats	3,523 beats
Accelerated idioventricular rhythms	0-33 episodes	2 episodes	5 episodes
Triplets	0-18 episodes	10 episodes	32 episodes
Couplets	0-3,187 episodes	124 episodes	361 episodes
Bigeminy	0-3,187 episodes	116 episodes	403 episodes
Trigeminy	0-1,144 episodes	93 episodes	349 episodes
Maximum ectopic beats per hour	0-1,501 beats	259 beats	350 beats

Table 4. Ventricular Ectopy by Gender

Type of ectopy	**Women** *Mean (SD)*	**Men** *Mean (SD)*
Total ventricular ectopy (24 hr)	2,296 (4,426) beats	2,372 (3,784) beats
Accelerated idioventricular rhythms	0 episodes	3 (6) episodes
Triplets	0.25 (0.5) episodes	12 (35) episodes
Couplets	78.75 (158) episodes	141 (404) episodes
Bigeminy	169 (337) episodes	134 (512) episodes
Trigeminy	286 (572) episodes	73 (170) episodes
Maximum ectopic beats per hour	221 (399) beats	252 (342) beats

Table 5. Ventricular Ectopy by Race

Type of ectopy	Caucasian	African-American	Hispanic
Total ventricular ectopy (24 hr)	2,229 (3,551) beats	4,980 (7,041) beats	92 (120) beats
Accelerated idioventricular rhythms	2 (6) episodes	5 (8) episodes	0 (0) episodes
Triplets	10 (30) episodes	35 (69) episodes	0 (0) episodes
Couplets	111 (323) episodes	459 (900) episodes	2 (2) episodes
Bigeminy	153 (561) episodes	107 (134) episodes	0 (0) episodes
Trigeminy	95 (258) episodes	129 (93) episodes	0 (0) episodes
Maximum ectopy per hour	239 (343) beats	457 (495) beats	11 (12) beats

Table 6. Type of Myocardial Infarction Experienced by Participants

Type of Infarct	Percent with History
Anterior	30%
Inferior	40%
Lateral	11%
Apical	2%
Septal	14%

Table 7. Medication Titration

Type of Drug	Withheld	Continued	Not prescribed
Beta blocker	21%	60%	19%
Calcium blocker	5%	4%	91%
ACE inhibitor	3%	60%	37%
Nitrate	2%	23%	75%
Amiodarone	0%	4%	96%
Sotalol	0%	4%	96%
Other antiarrhythmic	0%	9%	91%

Table 8. Measures of Heart Rate Variability in patients with implantable cardioverter defibrillators (ICD), non-arrhythmia prone patients with coronary artery disease (CAD) and healthy controls.

	ICDs	**CADs**	**Healthy Controls**
SDNN	111 (41)	141 (50)	131 (29)
ASDNN	52 (28)	58 (18)	59 (19)
SDANN5	93 (34)	124 (50)	115 (31)
RMSSD	37 (44)	33 (25)	32 (19)

Table 9. Zero-order Correlations between Beck Depression Inventory scores and arrhythmias in patients with ejection fractions > 30.

Accelerated idioventricular rhythms	r = -.43	p = .07
Episodes of bigeminy	r = -.408	p = .08
Couplets	r = -.412	p = .08
Single PVCs	r = -.431	p = .07
Total ectopy	r = -.422	p = .07

Table 10. Correlations between Beck Depression Inventory scores and arrhythmias in patients with ejection fractions < 30.

Accelerated idioventricular rhythms	r = -.771	p = .07
Episodes of bigeminy	r = -.686	p = .13
Couplets	r = -.60	p = .21
Single PVCs	r = -.765	p = .08
Total ectopy	r = -.757	p = .08

Table 11. Zero-order correlations between physical activity and ventricular ectopy.

	Light activity	Moderate activity	Vigorous activity	Heavy activity	Extreme activity
Accelerated idioventricular rhythm	*r* = -.039 p = .87	*r* = .341 p = .11	*r* = .271 p = .22	*r* = -.265 p = .27	*r* = -.219 p = .37
Episodes of bigeminy	*r* = .022 p =.93	*r* = .39 p = .06	*r* = .006 p = .98	*r* = -.33 p = .16	*r* = -.242 p = .31
Couplets	*r* = -.003 p = .99	*r* = .447 P = .03	*r* = .136 p = .55	*r* = -.19 p = .43	*r* = -.279 p = .25
Single PVCs	*r* = .081 p = .73	*r* = .39 p = .06	*r* = .174 p = .44	*r* = -.186 p = .45	*r* = -.312 p = .19
Total 24-hour ectopy	*r* = .074 p = .75	*r* = .388 p = .07	*r* = .166 p = .46	*r* = -.179 p = .46	*r* = -.31 p = .20

Table 12. Partial correlations between usual levels of activity and arrhythmia, controlling for ejection fraction

	Light activity	Moderate activity	Vigorous activity	Heavy activity	Extreme activity
Accelerated idioventricular rhythm	*r* = .023 p = .93	*r* = .362 p = .17	*r* = -.124 p = .65	*r* = -.235 p = .38	*r* = -.221 p = .41
Episodes of bigeminy	*r* = -.05 p =.85	*r* = .30 p = .25	*r* = -.223 p = .39	*r* = -.20 p = ..47	*r* = -.15 p = .58
Couplets	*r* = .053 p = .84	*r* = .412 P = .11	*r* =-.20 p = .46	*r* = -.04 p = .89	*r* = -.27 p = .31
Total 24-hour ectopy	*r* = .074 p = .78	*r* = .43 p = .09	*r* = -.275 p = .30	*r* = -.022 p = .94	*r* = -.228 p = .40

Table 13. Zero-order correlations between physical activity and measures of heart rate variability.

	24-hr VLF	**24-hr LF**	**24-hr HF**	**24-hr LF/HF**	**SDNN**	**SDANN**	**ASDNN**	**RMSSD**
Light Activity	R = -.266 P = .25	R = -.34 P = .13	R = -.077 P = .74	R = -.354 P = .12	R = .113 P = .63	R = .182 P = .43	R = -.206 P = .37	R = -.048 P = .83
Moderate Activity	R = -.217 P = .34	R = -.11 P = .63	R = -.015 P = .95	R = -.086 P = .71	R = -.020 P = .93	R = .045 P = .85	R = -.105 P = .65	R = .071 P = .76
Vigorous Activity	R = -.210 P = .36	R = .025 P = .91	R = .115 P = .61	R = -.057 P = .80	R = -.004 P = .98	R = -.005 P = .98	R = -.015 P = .94	R = .246 P = .42
Heavy Activity	R = .113 P = .65	R = -.006 P = .98	R = -.188 P = .44	R = .194 P = .43	R = .028 P = .91	R = .047 P = .85	R = -.093 P = .71	R = -.193 P = .42
Extreme Activity	R = .050 P = .84	R = .068 P = .78	R = -.158 P = .52	R = .265 P = .27	R = -.246 P = .22	R = -.296 P = .22	R = -.116 P = .64	R = -.151 P = .538

Table 14. Correlations between Beck Depression Inventory scores and heart rate variability

Very Low Frequency	r = -.57	p = .24
Low Frequency	r = -.62	p = .14
High Frequency	r = -.67	p = .10
SDNN	r = -.77	p = .04
SDNN5	r = -.81	p = .03
ASDNN	r = -.69	p = .09
RMSSD	r = -.83	p = .02

Table 15. Zero-order correlations between 24-hour HRV and arrhythmia.

	VLF	LF	HF	L/H	RMSSD	ASDNN	SDANN5	SDNN
Single PVCs	r = -.04 p = .80	r = .25 p = .10	r = .12 p = .47	r = .11 p = .51	r = .18 p = .26	r = .05 p = .77	r = .25 p = .11	r = .11 p = .50
Couplets	r = -.01 p = .94	r = .19 p = .21	r = .06 p = .73	r = .13 p = .40	r = .16 p = .30	r = .04 p = .81	r = .18 p = .25	r = .07 p = .66
Bigeminy	r = -.01 p = .94	r = .15 p = .35	r = .06 p = .73	r = .10 p = .55	r = .14 p = .36	r = .25 p = .10	r = .11 p = .50	r = .25 p = .12
Accelerated idioventricular rhythm	r = -.13 p = .42	r = .15 p = .35	r = .07 p = .67	r = .08 p = .62	r = .16 p = .30	r = -.12 p = .46	r = .17 p = .28	r = -.05 p = .74

Table 16. Zero-order correlations between BDI-II scores and HRV in patients with ejection fractions less than 30.

24-hour very low frequency	r = -.57	p = .24
24-hour low frequency	r = -.62	p = .14
24-hour high frequency	r = -.67	p = .10
24-hour low/high frequency ratio	r = -.45	p = .32
SDNN	r = -.77	p = .04
ASDNN	r = -.81	p = .03
ASDNN5	r = -.69	p = .09
RMSSD	r = -.83	p = .02

Table 17. Summary of Hypotheses.

1a. Acute Negative Emotions and Arrhythmia	Supported
1b. Acute Physical Activity and Arrhythmia	Not supported
2a. Chronic Psychological Factors and Arrhythmia	Not supported
2b. Usual Levels of Physical Activity and Arrhythmia	Not supported
3a. Acute Negative Emotions and Heart Rate Variability	Not supported
3b. Chronic Psychological Factors, Usual Levels of Physical Activity, and Heart Rate Variability	Supported for psychological factors Not supported for physical activity
3c. Heart Rate Variability prior to Arrhythmic Events	Supported
3d. 24-Hour Heart Rate Variability and Arrhythmia	Not supported

Figure 1. Beck Depression Inventory Scores and Total 24-Hour Ventricular Ectopy

(r = -.452, p = .02)

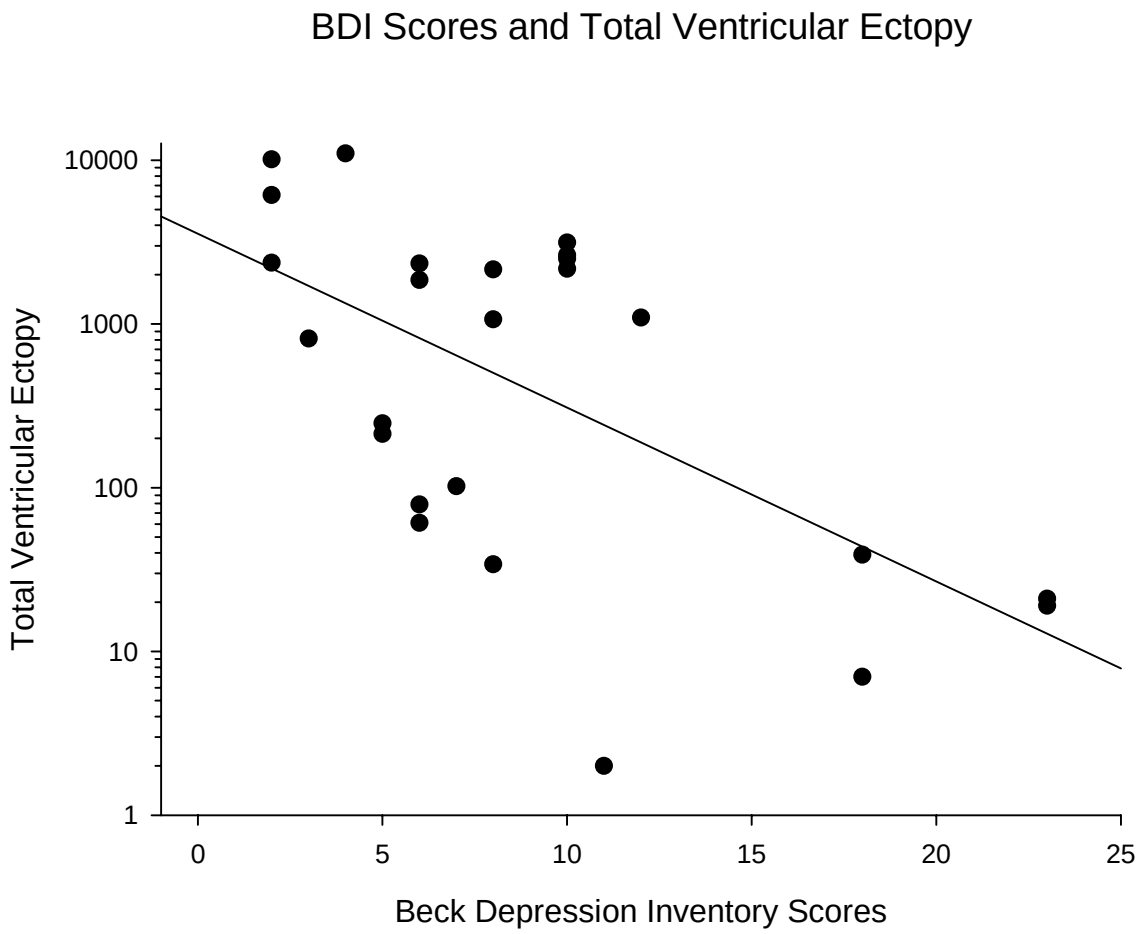


Figure 2. Correlation between BDI-II Scores and Episodes of Trigeminy (r = -.29, p = .03)

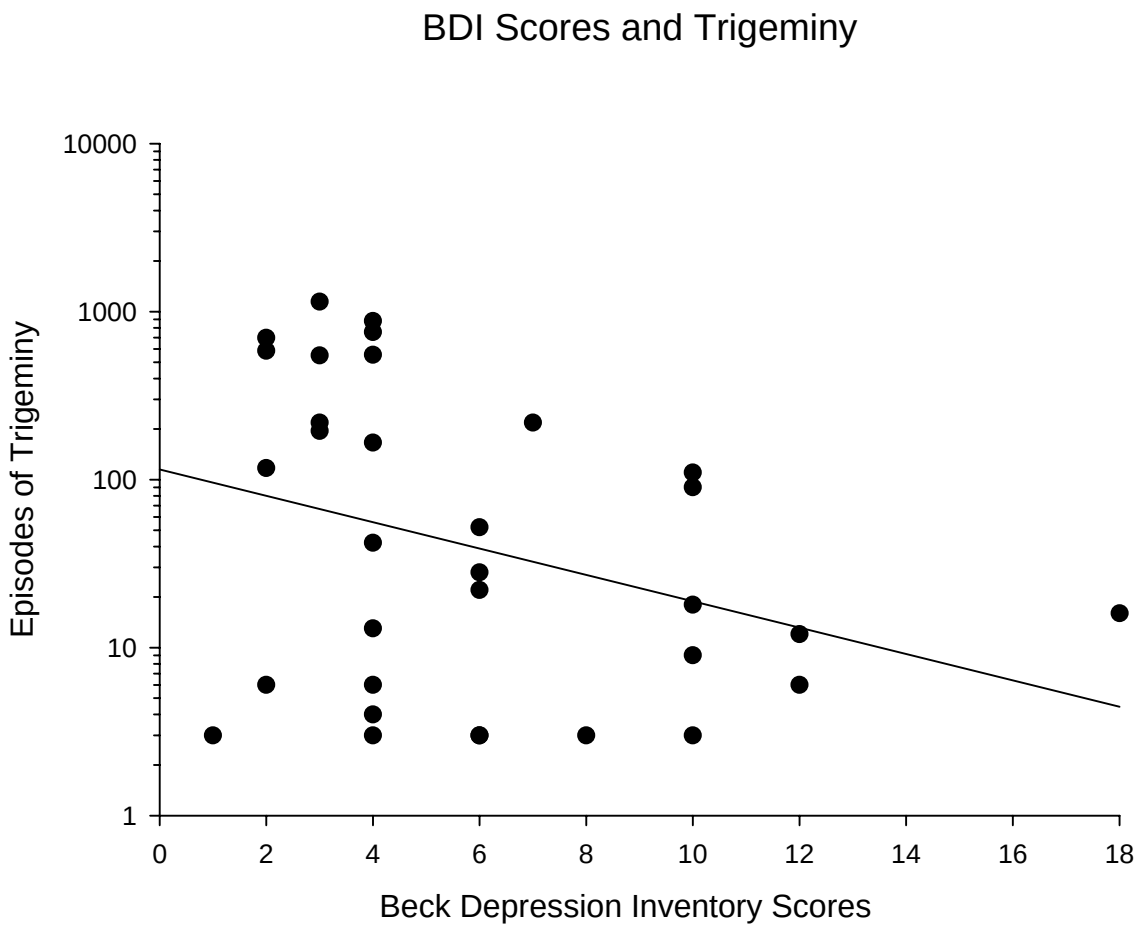


Figure 3. Depression and Single PVCs (*r* = -.46, p = .02)

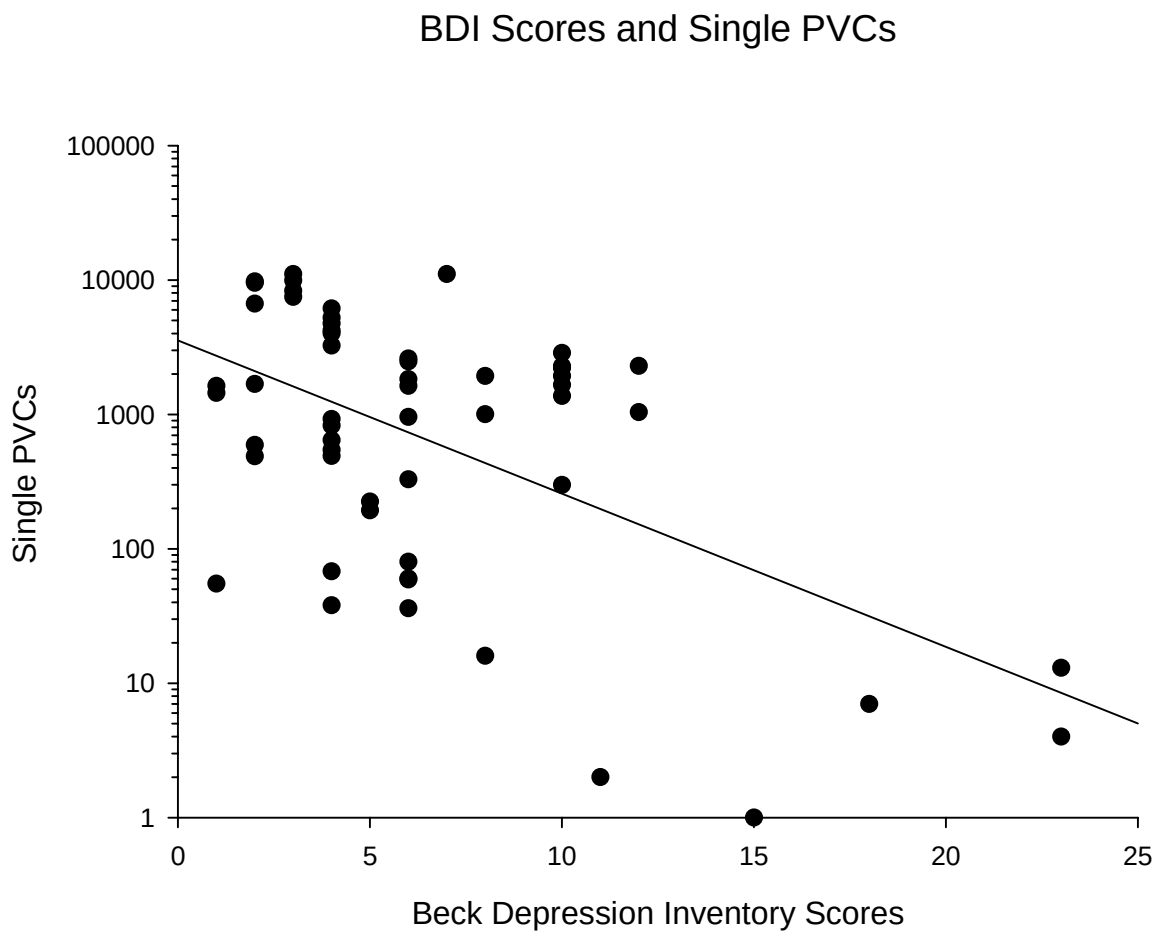


Figure 4. BDI-II Scores and Maximum Ectopy per Hour (r = -.38, p = .004)

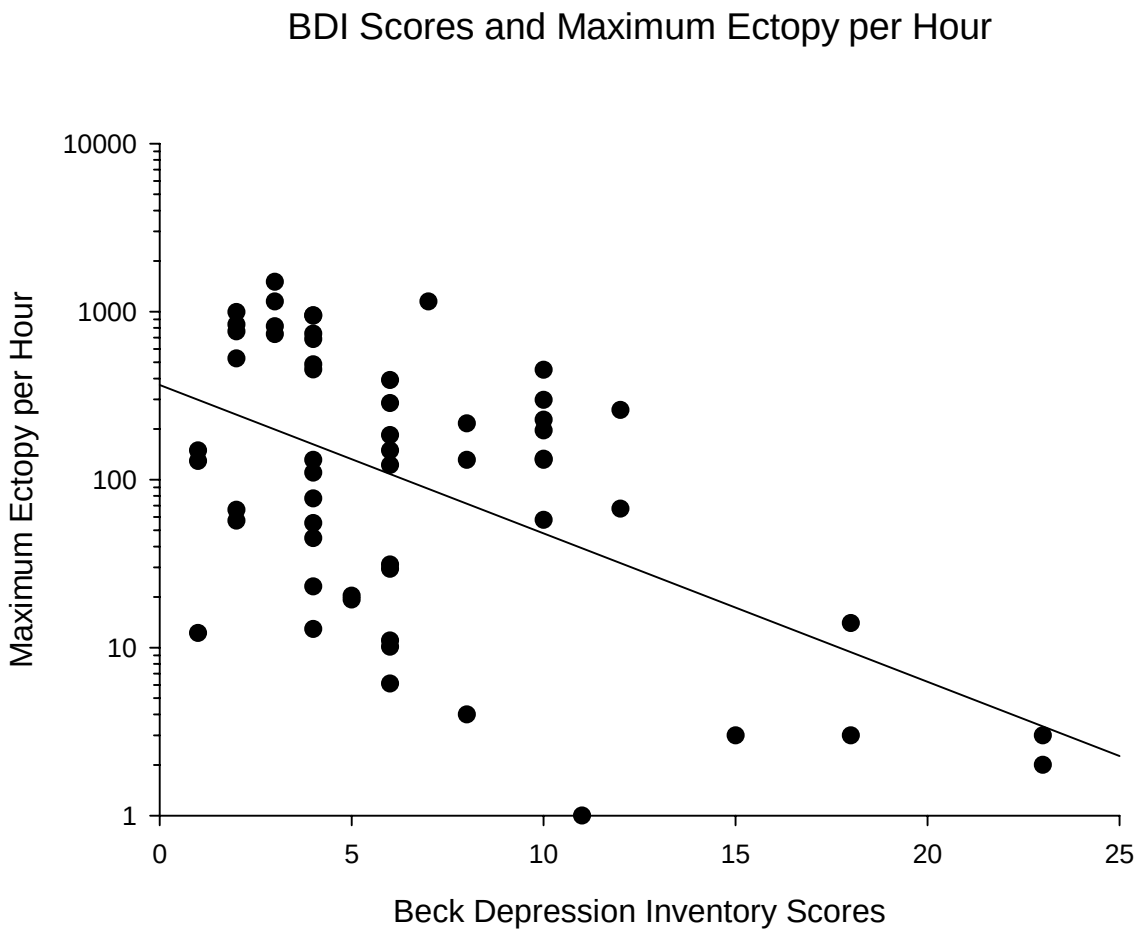


Figure 5. BDI-II Scores and Couplets (r = -.41, p = .04)

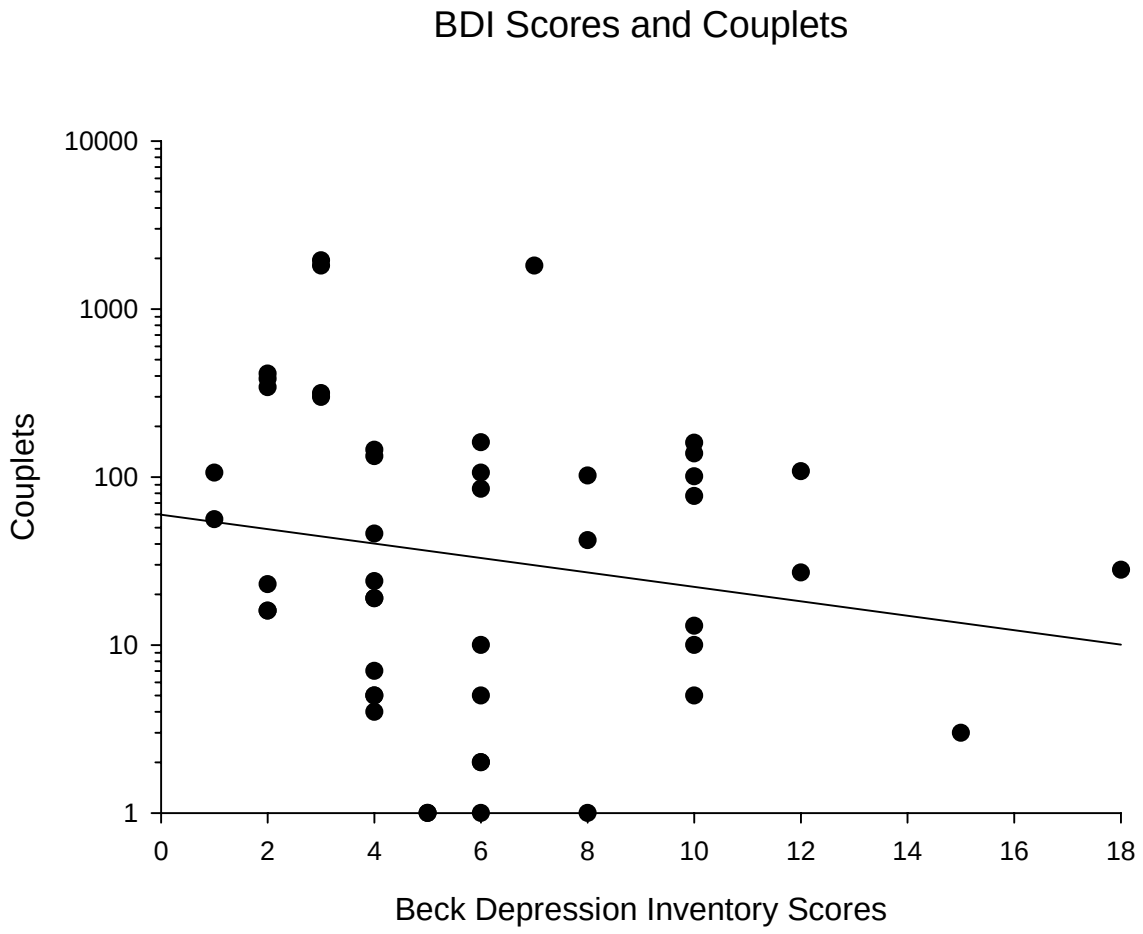


Figure 6. BDI-II Scores and Bigeminy (r = -.39, p = .05)

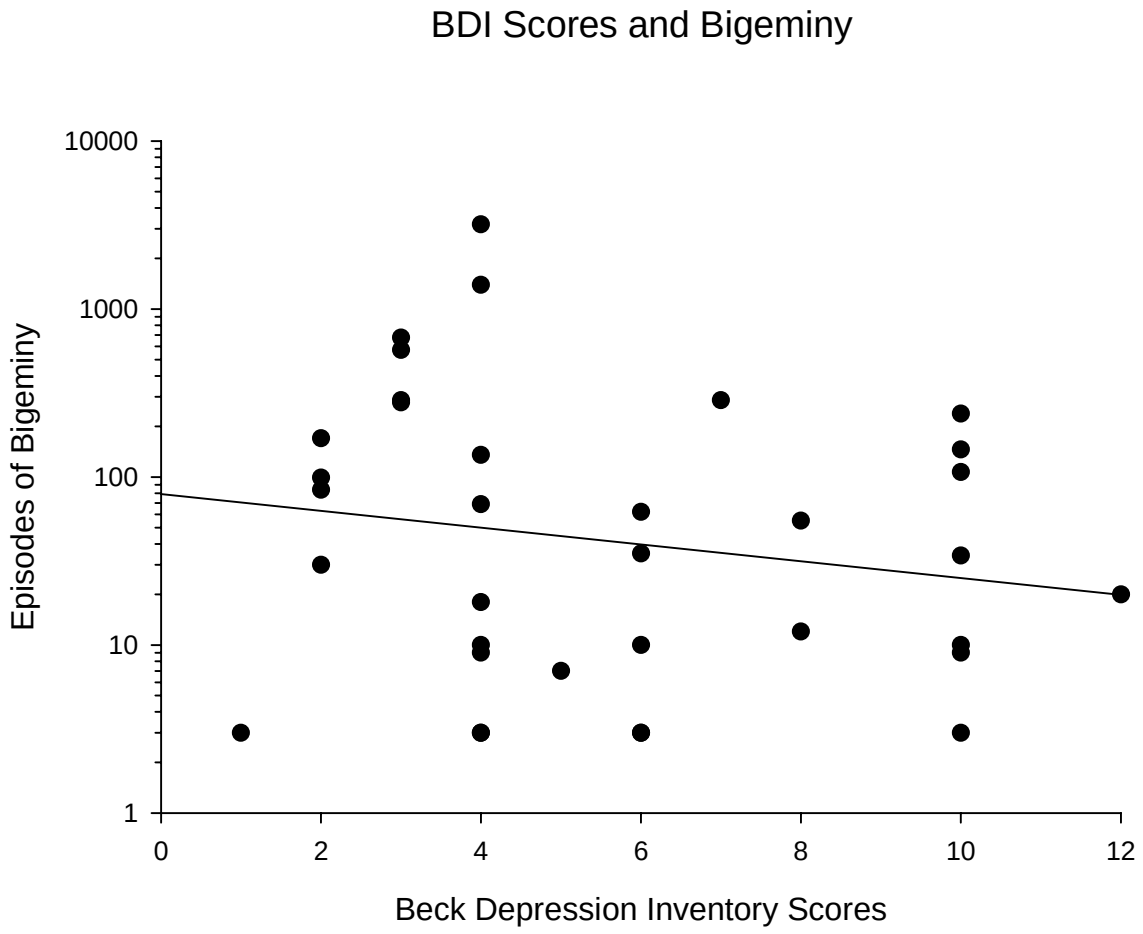


Figure 7. Hostility and Accelerated Idioventricular Rhythm

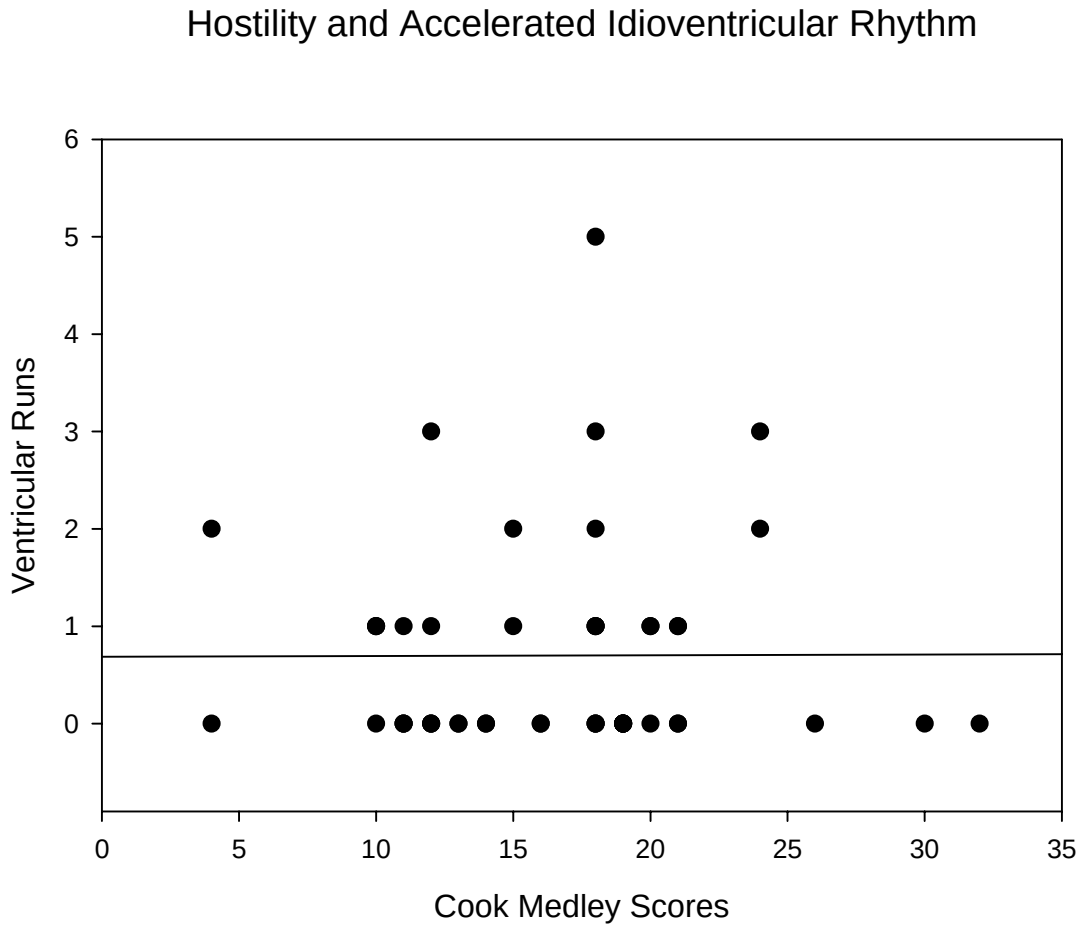


Figure 8. Hostility and Total 24-Hour Ectopy

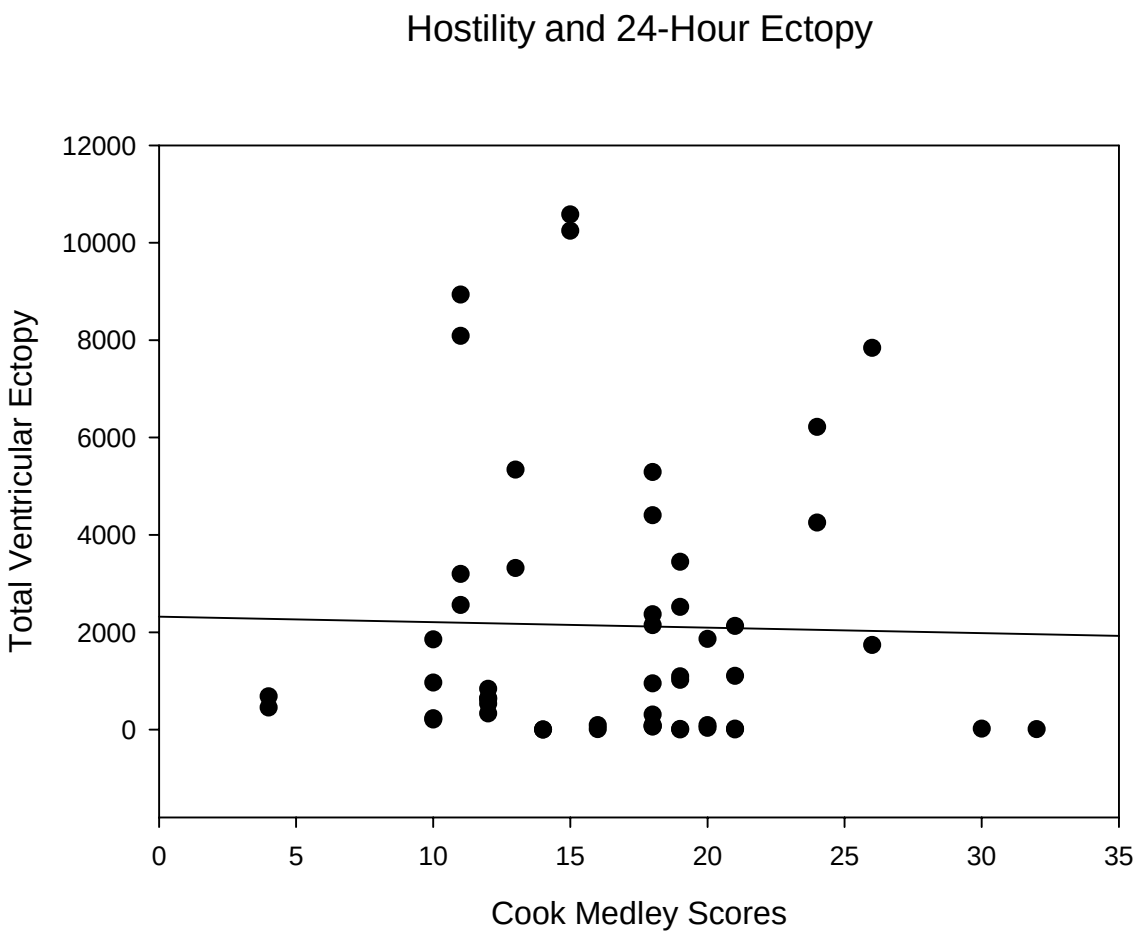


Figure 9. Anxiety and 24-Hour Ectopy (r = .05, p = .82)

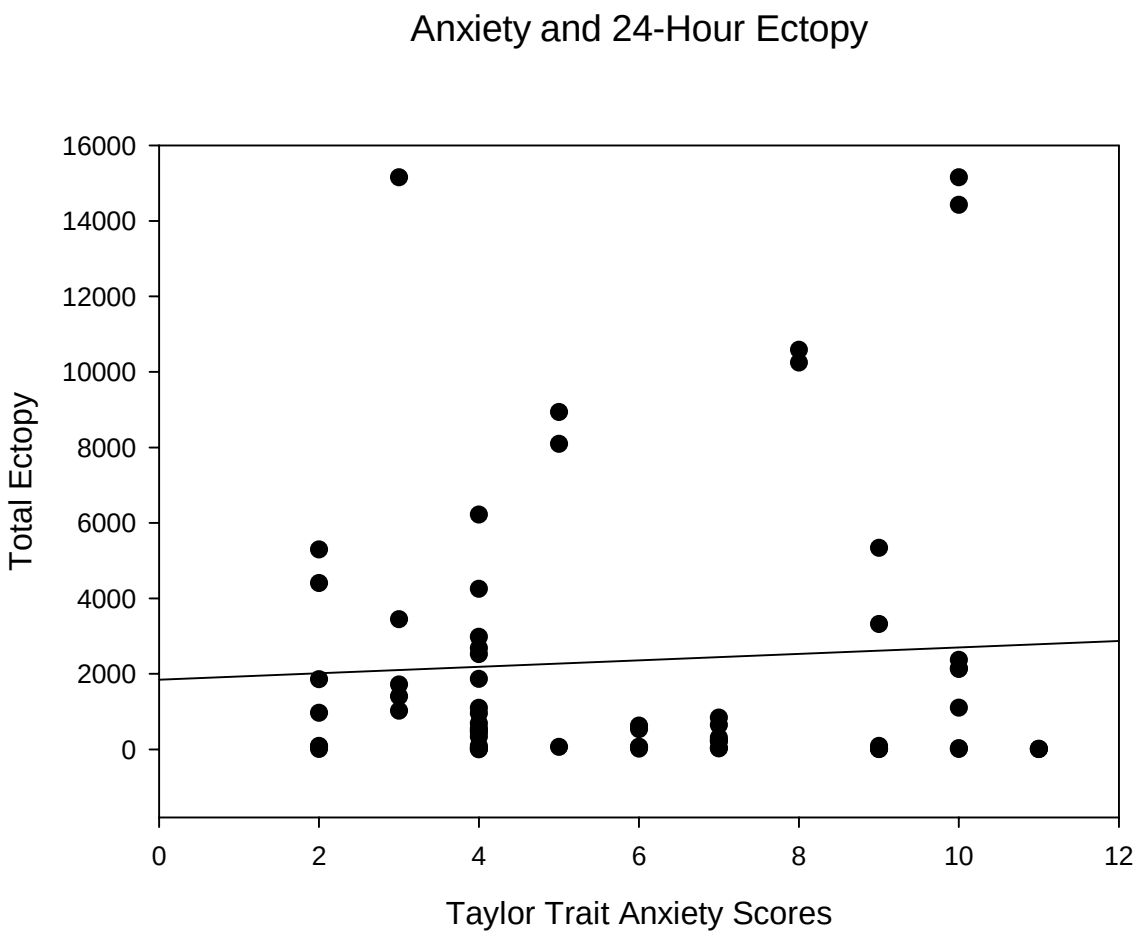


Figure 10. Anxiety and Single PVCs (r = .03, p = .87)

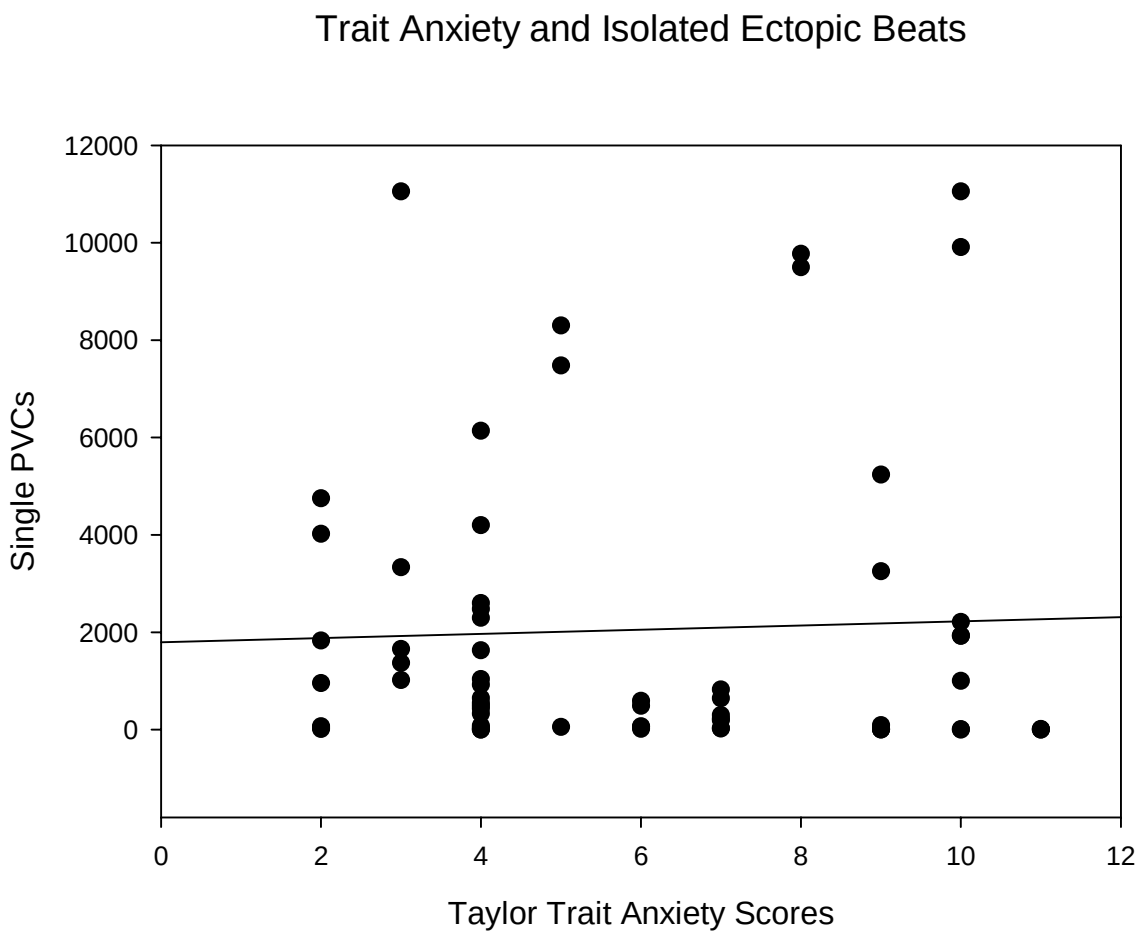


Figure 11. Usual Level of Moderate Activity and Couplets (r = .45, p = .03)

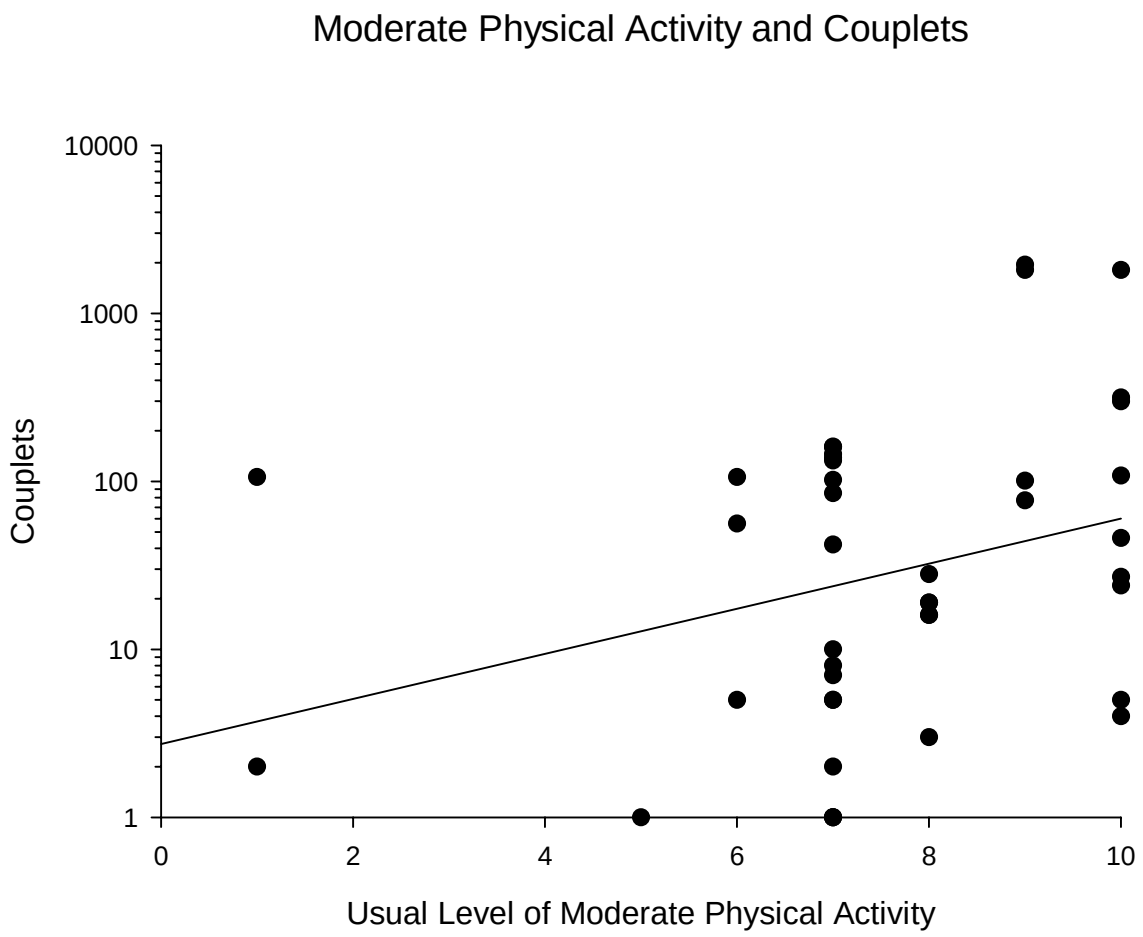


Figure 12. Usual Level of Moderate Physical Activity and Single PVCs (r = .39, p = .06)

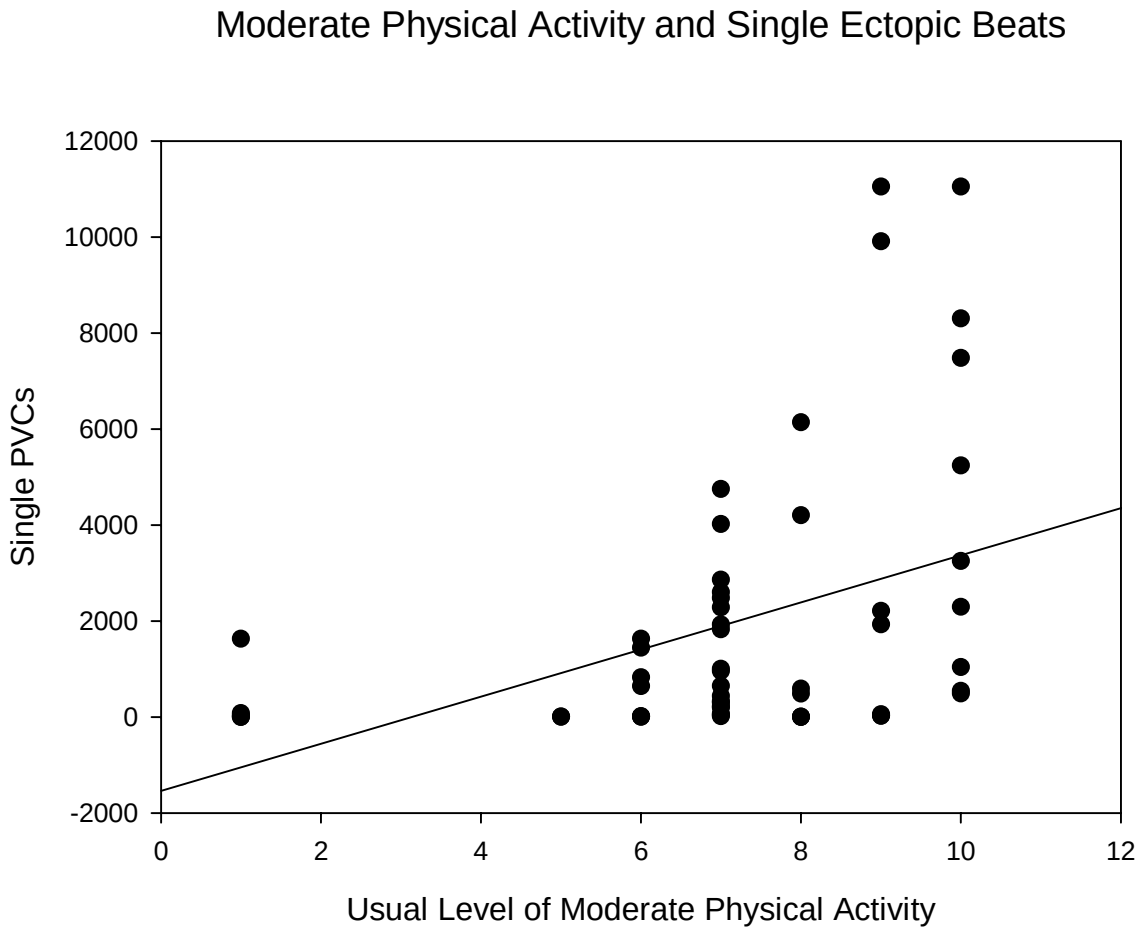


Figure 13. Usual Level of Moderate Physical Activity and Episodes of Bigeminy (r = .39, p = .06)

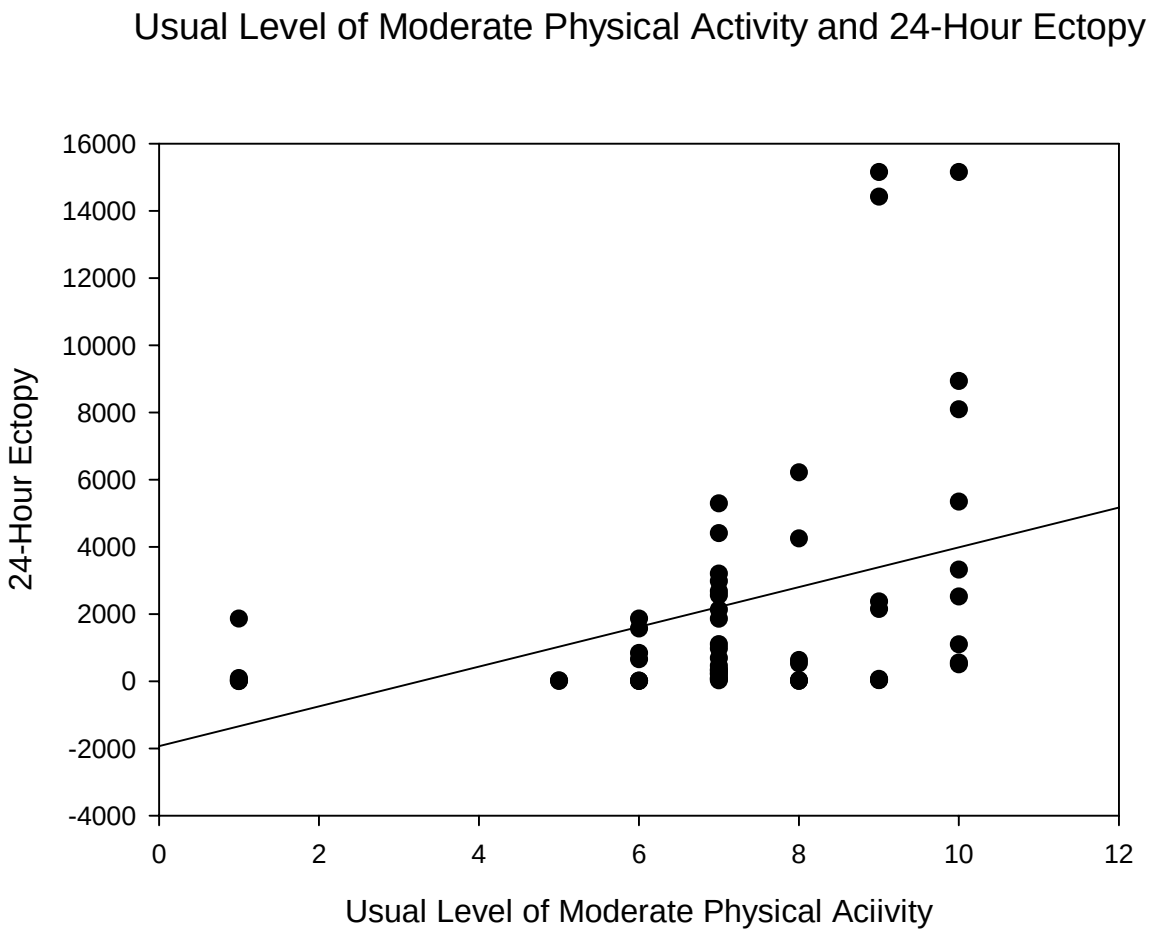


Figure 14. Usual Level of Moderate Physical Activity and Accelerated Idioventricular Rhythm (r = .34, p = .11)

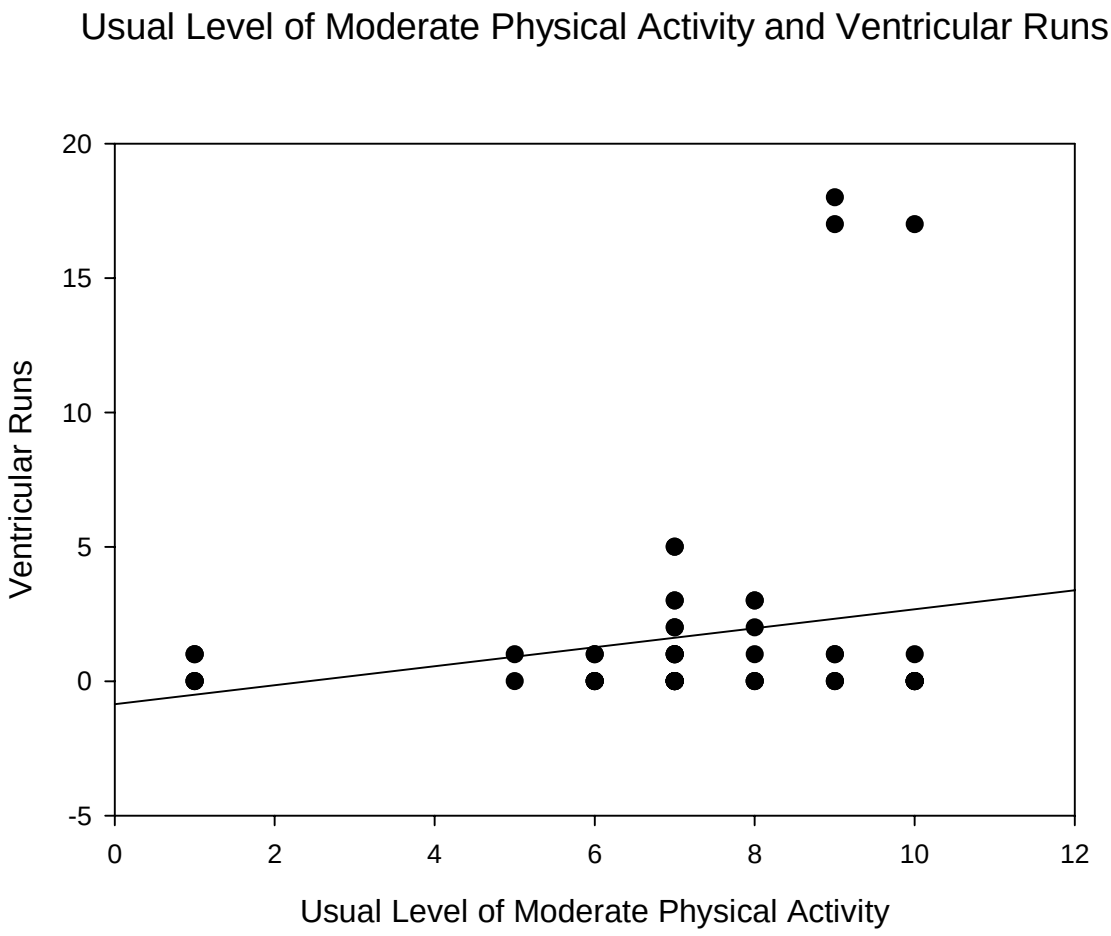


Figure 15. Changes in HRV following negative emotions

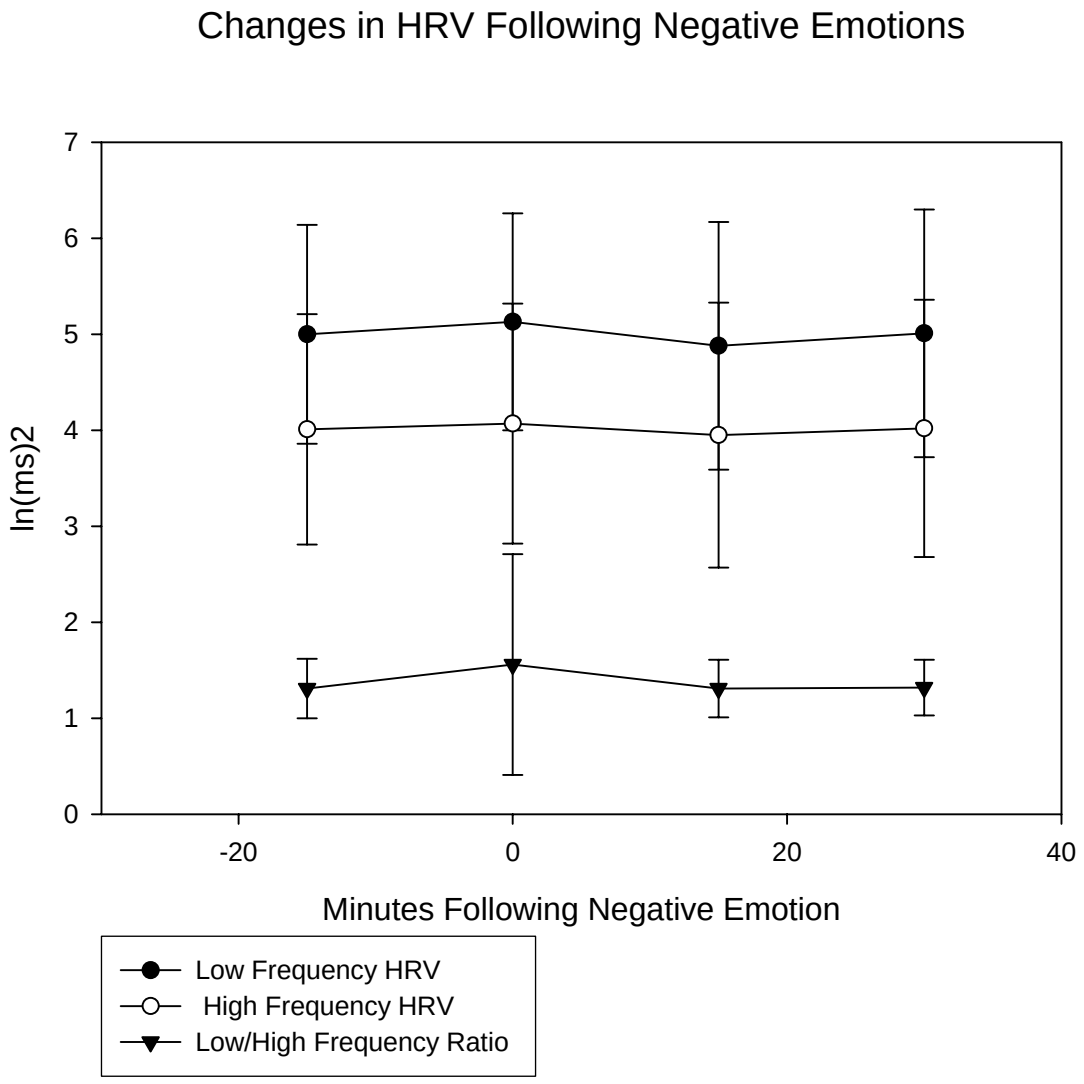


Figure 16. Trait anxiety and SDNN (r = -.42, p = .04)

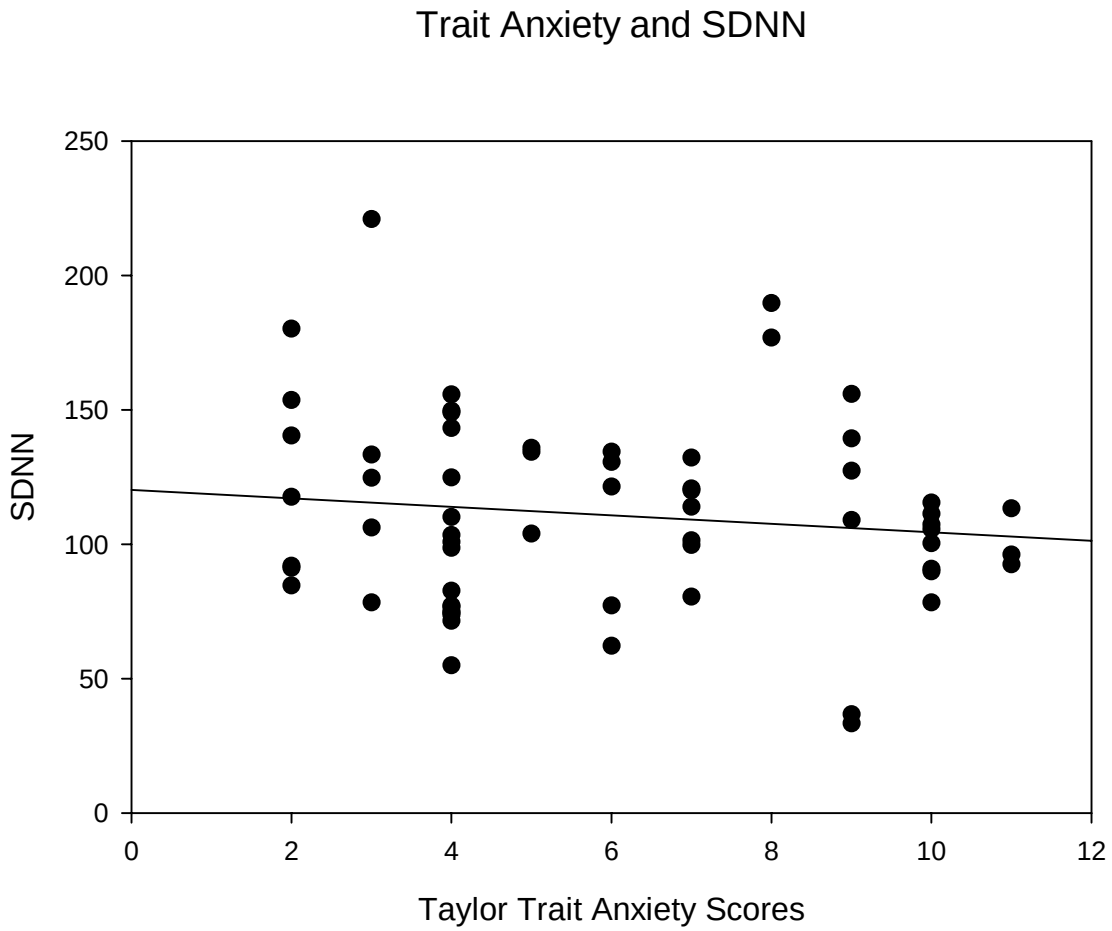


Figure 17. BDI-II Scores and 24-Hour High Frequency HRV (r = -.42, p = .04)

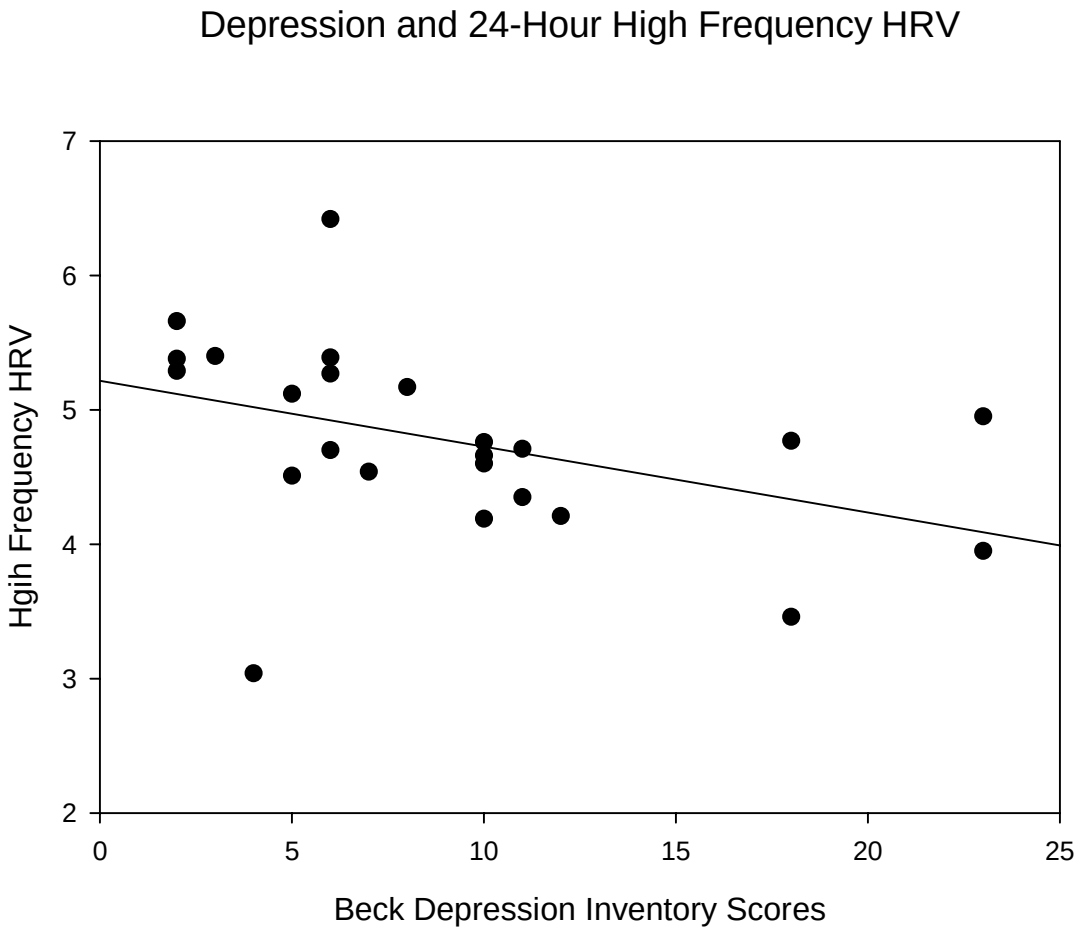


Figure 18. Hostility and ASDNN (r = -.14, p = .31)

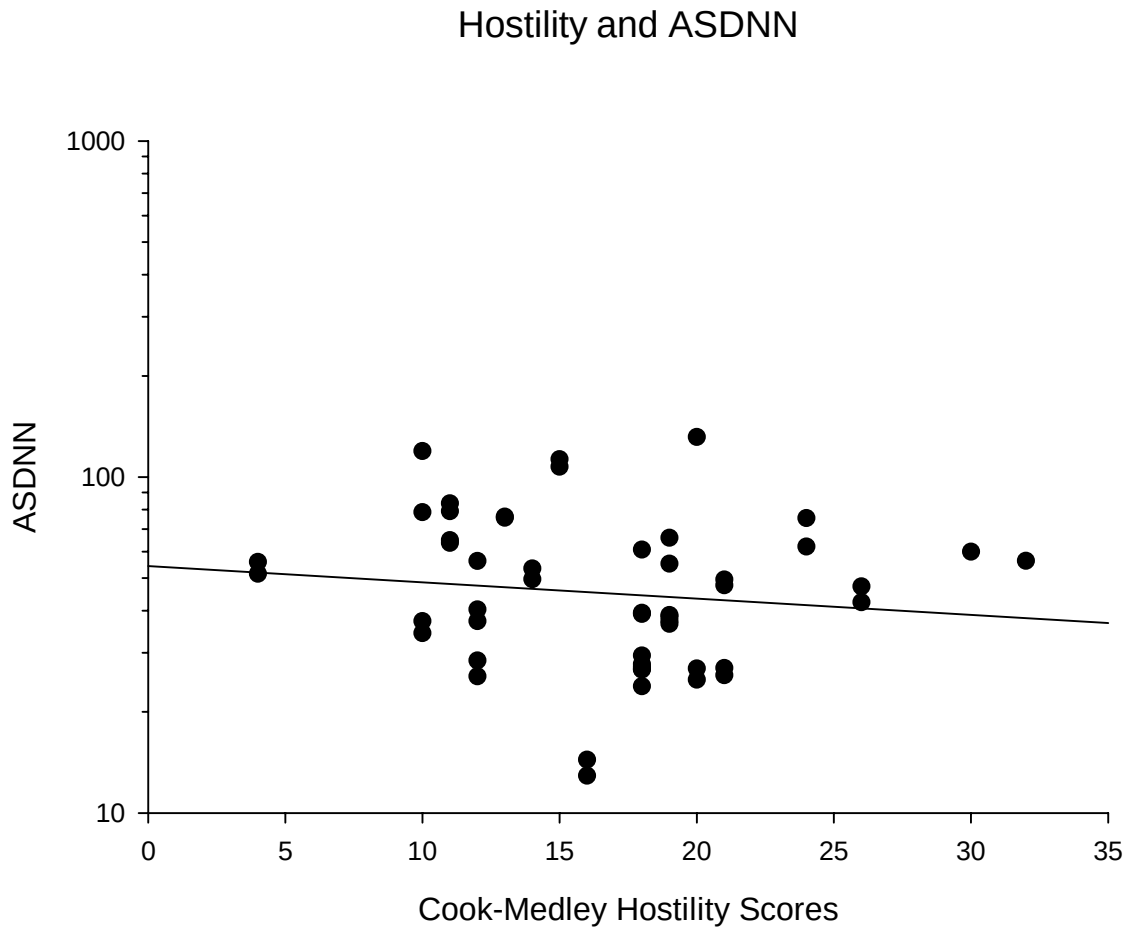


Figure 19. Hostility and SDNN (r = -.16, p = .27)

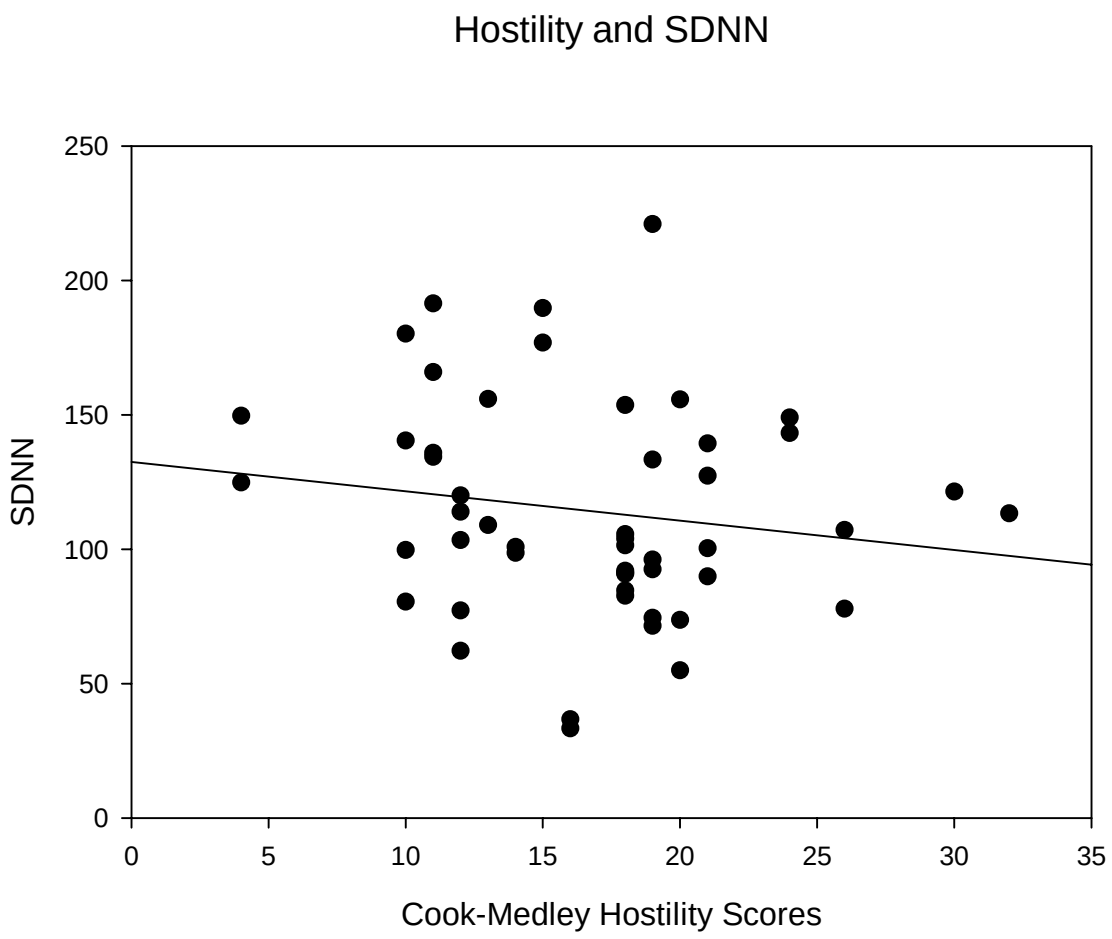


Figure 20. Usual Level of Moderate Activity and SDNN

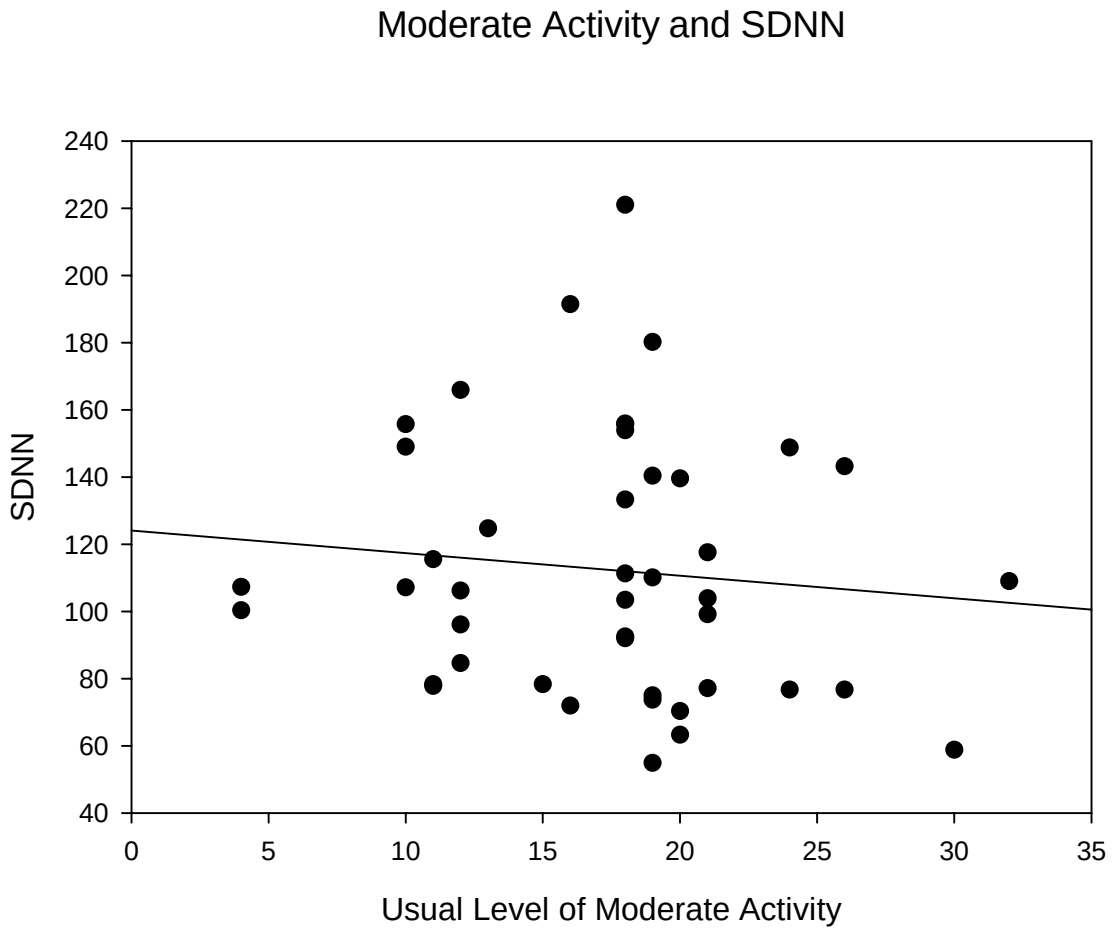


Figure 21. Usual Level of Vigorous Activity and ASDNN

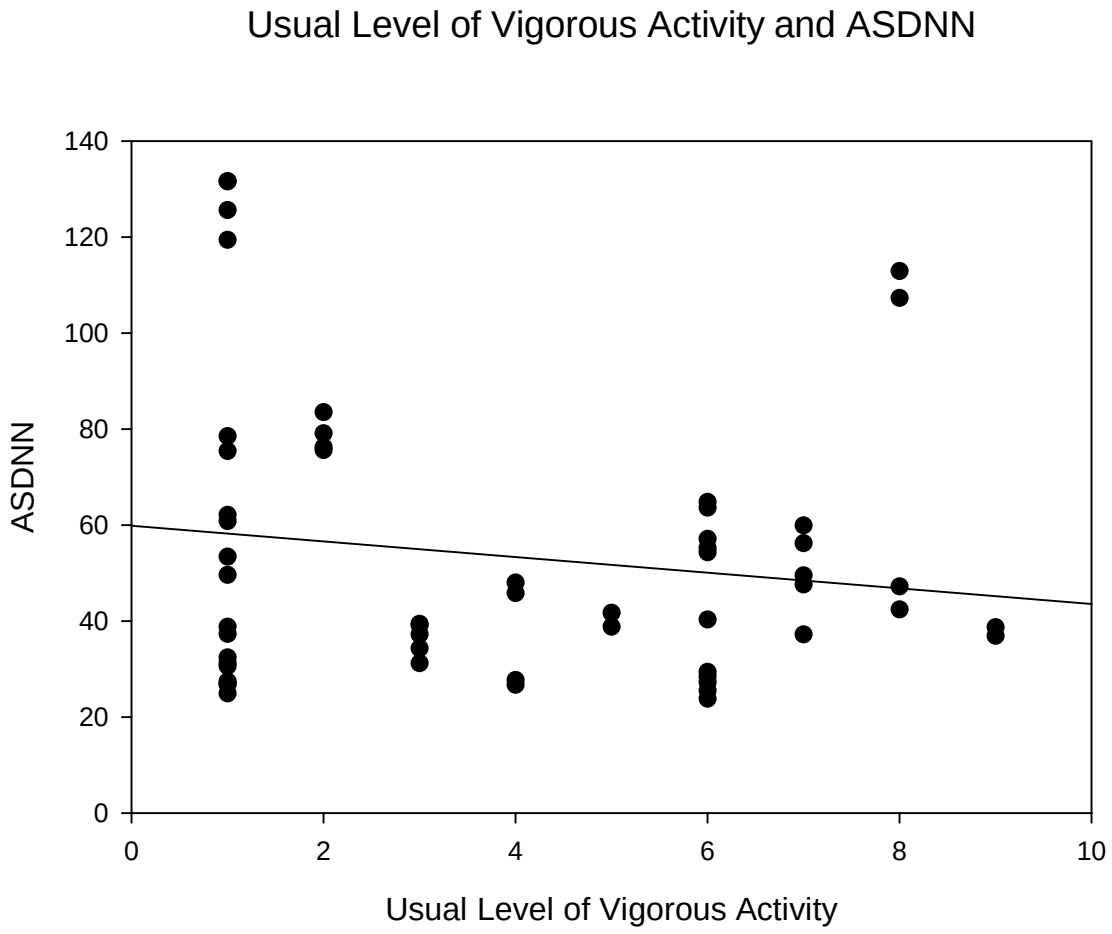


Figure 22. Changes in Low-Frequency HRV Prior to Arrhythmia (Couplets Excluded) ($F(3,120) = 2.36$, $p = .07$)

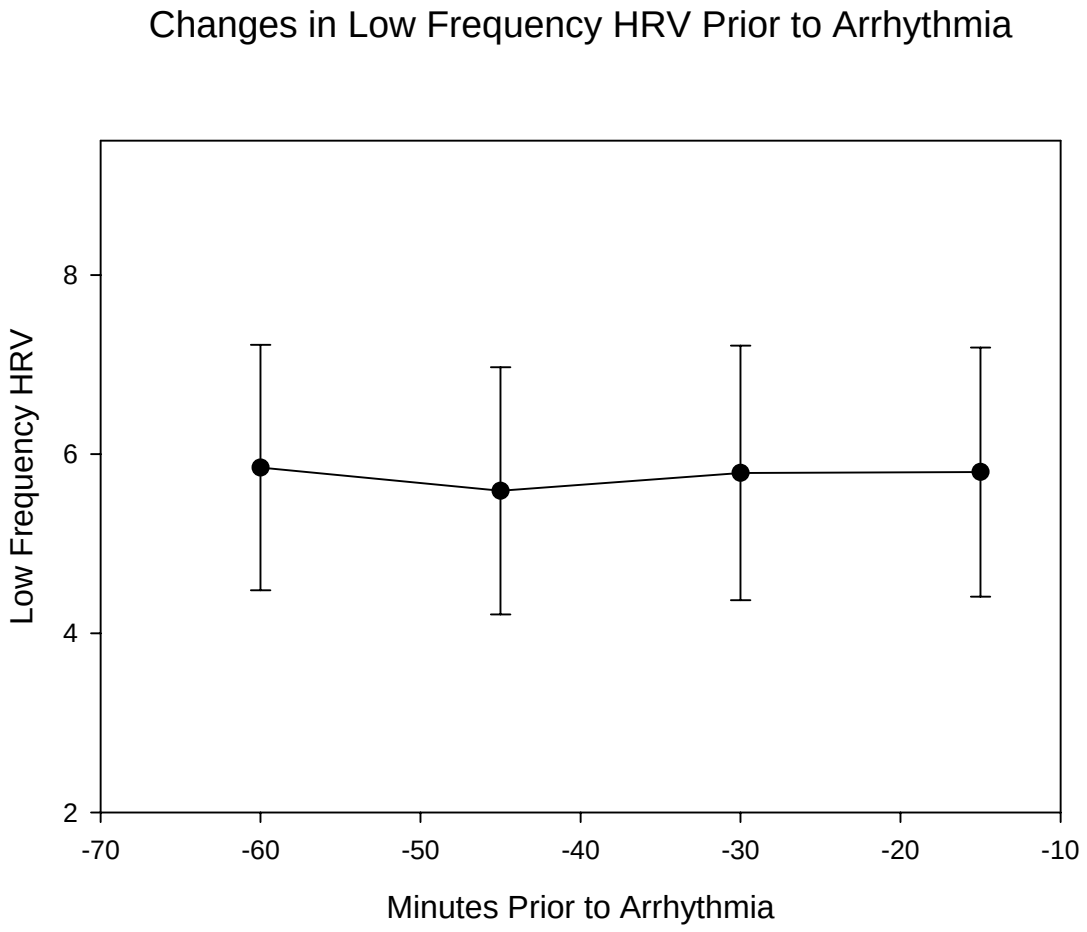


Figure 23. Changes in Low/High Frequency Ratio Prior to Accelerated Idioventricular Rhythm

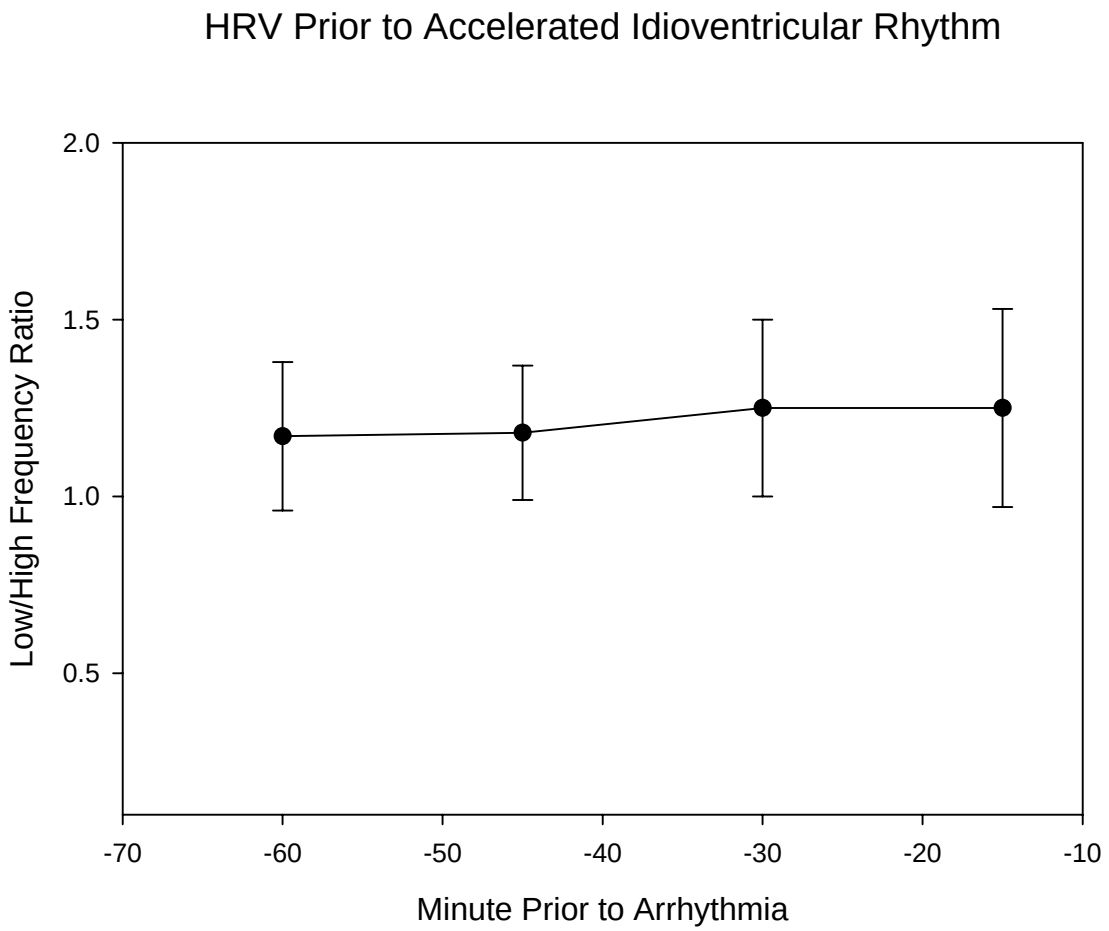


Figure 24. SDNN and Frequency of Accelerated Idioventricular Rhythm (r = -.17, p = .13)

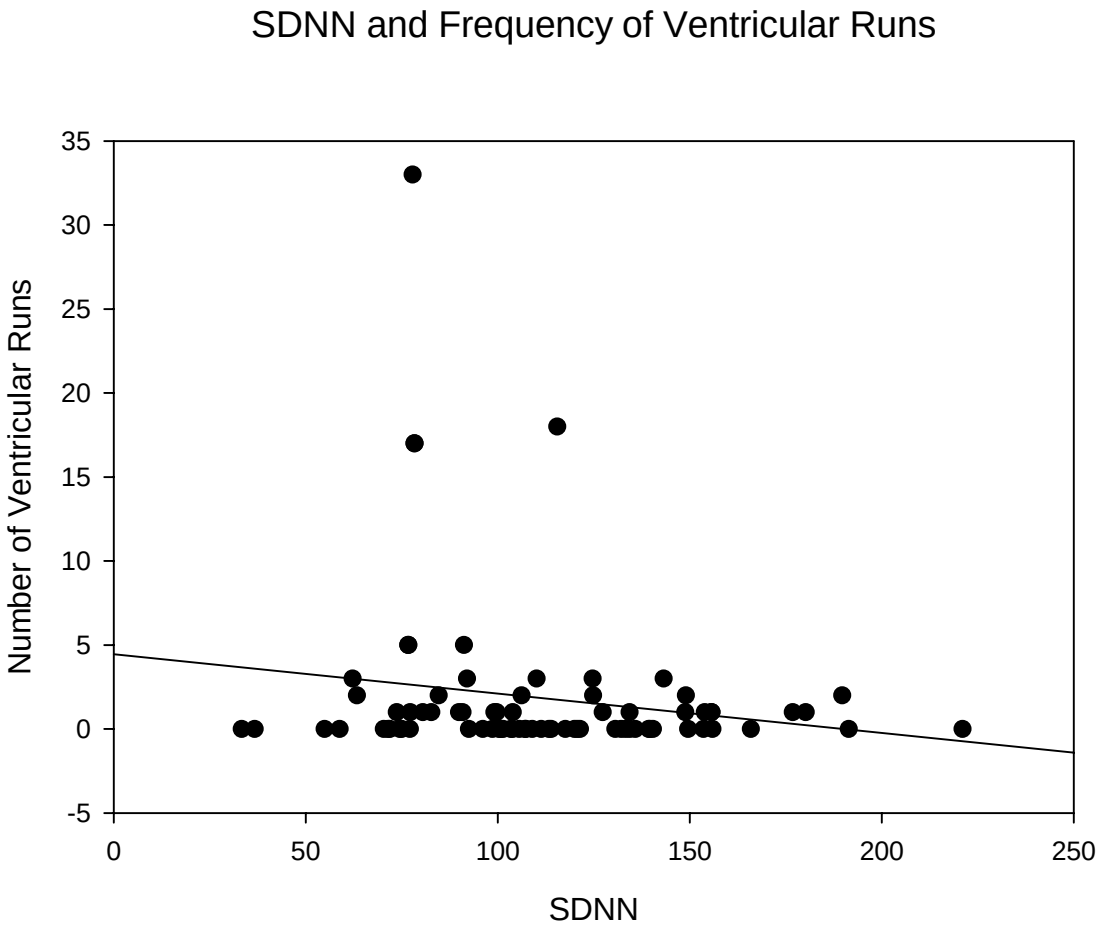
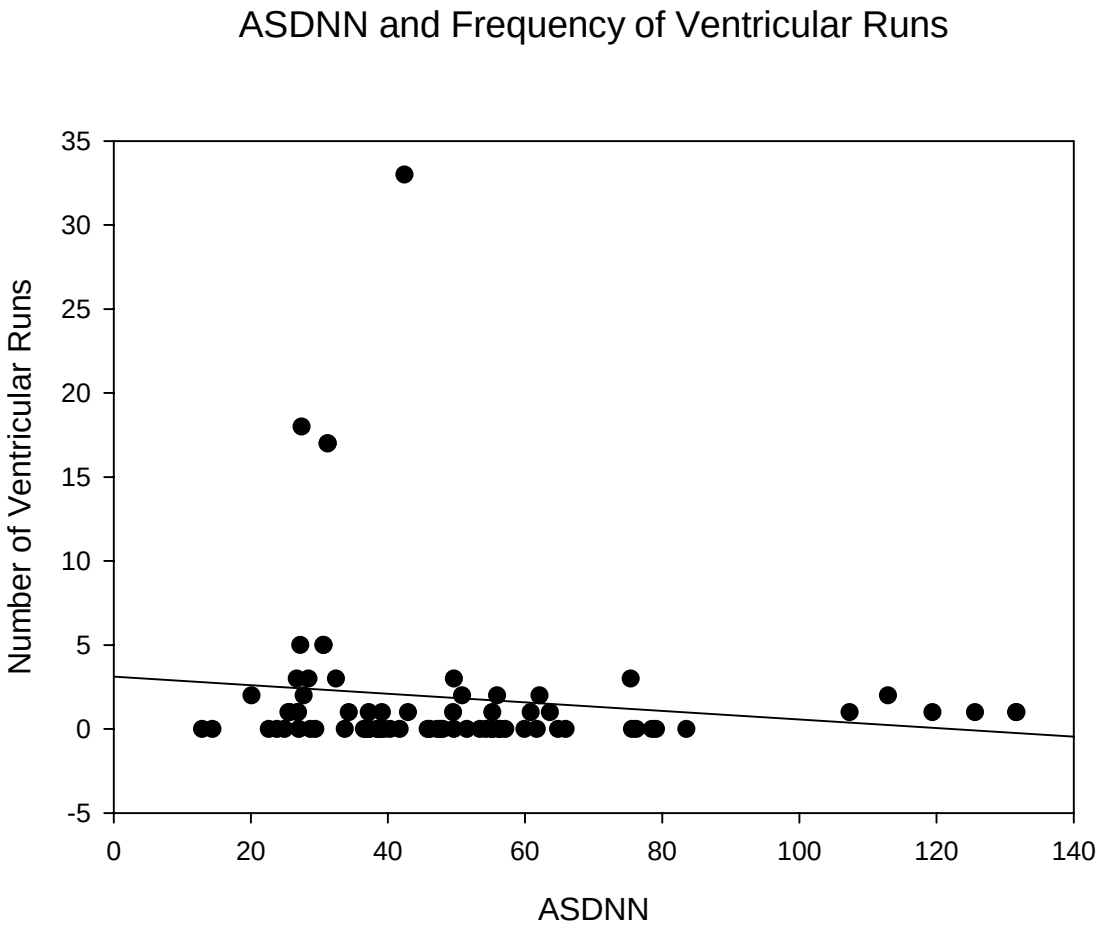


Figure 25. ASDNN and Frequency of Accelerated Idioventricular Rhythm (r = -.14, p = .24)



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DIARY INSTRUCTIONS

- Please complete the cover of each diary, particularly the time you awake and how restful your sleep was.
- Circle the time activity starts and stops. If we give you a watch for this study, please use the exact time of that watch. There should not be time gaps between pages.
- Each change of activity should be listed on a separate page. Sometimes you will have multiple entries on the same diary page, i.e.eating/drinking and reading the paper.
- **The right side of the page is as important as the left side.**
- Please indicate your posture and whether or not you were alone during the activity.
- Completing the physical and mental effort scale will help us understand the level of activity that effects your heart.
- Completing the section on emotional status allows us to look at the relationship between your mood and heart function.

Be sure to note the following:

1. Wear the watch we gave you during the entire time you are wearing the Holter monitor.
2. Fill our a new sheet in the diary each time your emotions change OR your activites change.
3. Also, fill out a new sheet in the diary each time the beeper goes off (this occurs about 10 times during the day).
4. Each sheet of the diary can have more than one activity (i.e. eating, smoking, and talking) or only one activity (i.e. physical activity at work).
5. Make sure to rate each emotion. Do not just use "1's" or "5's". Use all of the numbers.
6. Fill our about 2-3 diary sheets per hour while awake.
7. Use the first diary for the first day, and the second diary for the second day.
8. Make sure you mark the time of awakening in your diary.

Activity Definitions:

going to sleep: lying down with intent to sleep; for nighttime and naptime.

rest: taking a deliberate break, physically and/or mentally, from the usual routine

washing/dressing: includes sponge bath and activities such as shaving and tooth brushing

driving/passenger: i.e. car travel; circle driving if you are behind the wheel, otherwise, passenger.

urination/defecation: indicate one or both as appropriate

eating drinking (non-alcohol): indicate which one of both; please note that caffeinated and alcoholic beverages are entered on a separate line as they can stimulate the heart.

smoking/caffeine/alcohol: indicate which one; caffeinated items can include coffee, tea, cola, chocolate (any of these items marked at "decaffeinated: would be circled under drinking

house activity: includes things like washing dishes, dusting, cooking, making bed; if greater than usual effort is made with some activities such as scrubbing floors on hands and knees, make sure you note it int eh physical effort section on the right side page.

walking/shopping: walking for any extended distance, length of time or requiring a fair amount of physical effort should be recorded; shopping includes groceries, clothing, etc.

stair climbing: may be in combination with other activity; please don't avoid stairs just because you have to fill out another page — it is an important activity to monitor.

sexual activity: includes everything from kissing to intercourse.

other physical activity: can include usual exercise routine if not covered by other items; you may want to state what it is in comment section

talking/listening: circle both when actively involved in conversation; listening may be to a lecture or sermon.

reading: newspapers, books, magazines, etc.

clerical/computer work: paying bills, writing letters, etc.

waiting: i.e. doctor's appointment, waiting for a telephone call, etc.

TV/radio: circle which one

thinking/worrying: includes active planning and daydreaming

other: anything you do that is different from printed activities

If you began or ended a diary page because the beeper prompted you to do so, check this off. Also, if you take nitro, indicate that and note the symptoms you had and the number of pills you took.

TIME___:___ AM/PM

POSTURE:
sit/stand/lying down

LOCATION:
home/work/other

BEEPED? yes/no

Since last entry, have you had any...
Tobacco: yes/no
_____cigs

Caffeine: yes/no
_____oz

Alcohol: yes/no
_____drinks

ACTIVITY

going to sleep
sleeping
rest
washing/dressing
urinating/defecating
driving/passenger
shopping
eating/drinking
house activity
walking
up/down stairs
sexual activity
talking/listening
reading
clerical work
TV/radio
thinking/concentrating
waiting
other:_____

AMOUNT OF EFFORT

	Not at all				Very much
physical	1	2	3	4	5
mental	1	2	3	4	5

MOOD

frustrated	1	2	3	4	5
tense	1	2	3	4	5
sad	1	2	3	4	5
happy	1	2	3	4	5
stressed	1	2	3	4	5
tired	1	2	3	4	5

HOW MUCH DO YOU FEEL...

chest pain	1	2	3	4	5
short of breath	1	2	3	4	5

CIRCLE ONE: alone/with others

HOW TO CARE FOR THE HOLTER MONITOR

- Once the chest leads are in place they must not be disturbed for 48 hours. They can be unhooked when the monitoring period is completed.

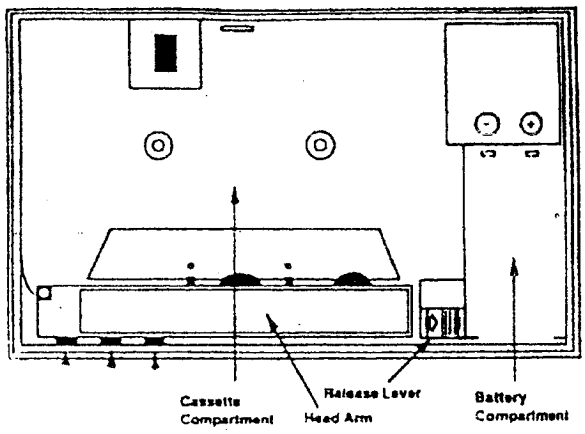
- The Holter monitor and leads cannot get wet. **This means that a shower or tub bath CANNOT be taken during the monitoring period.** You may take a sponge bath with care not to moisten or disturb the leads or machinery.

- The battery and tape within the Holter monitor will need to be changed after the first 24 hours of recording. To do so, remove the monitor from its carrying case and open the machine. First, remove the battery from it's compartment in the Holter monitor. This will stop recording. Then release the head arm which secures the cassette tape. The old tape can be removed safely at this point.

- Next, replace the battery with a fresh one, installing it in the same position as the used one.

- A new tape can now be inserted with the labeled side up and the head arm closed. Be sure that the head arm is completely closed or the monitor will not record your heart's activity. Check the time immediately and write the **exact** time on the diary. Place the monitor back in its carrying case.

- Here is a diagram of the inside of the monitor to assist with changing the battery and cassette tape:



- The actigraph monitor on your wrist should de kept dry as well. If possible, you should keep it on at night while you are asleep.

- The beeper may be removed and turned off for sleep but needs to be reactivated and worn during the day. The beeper should also be kept dry.

- When your 48 hours ends, unsnap the wires and then pull off the pads. The pads can be thrown away. Bring the monitor with wires, the case, beeper, diaries, tapes and actigraph back as arranged.

Brigham & Women's Hospital
AECG Core Laboratory
Neville House 3rd Floor
Boston, MA. 02115
Tel: 617-732-4860

PATIENT DEMOGRAPHIC DATA

Name: [redacted]
Source: TRIAD
ID Number: 12/13/00
Start Time: 12:40PM

Test Date: HL46
Scanned By: MAL
Patid:
Analysis Date: 07-08-01
Namecode:
Clinic:

Quality: VERY GOOD
Presence of Symptoms (Y/N)? :

ANALYSIS SUMMARY

Heart Rate Data

Total Beats: 68222
Min HR: 35 BPM at 7:05pm
Avg HR: 48 BPM
Max HR: 106 BPM at 12:25pm

Heart Rate Variability
(For Research Use Only)
ASDNN 5 : 56.7 msec
SDANN 5 : 70.2 msec
SDNN : 95.9 msec

Ventricular Ectopy

Total VE Beats.:	49
Vent Runs.....:	-
Beats.....:	-
Longest.....:	-
Fastest.....:	-
Triplets.....:	1 event
Couplets.....:	1 event
Single VEs.....:	44
R-on-T.....:	-
Late VEs.....:	1
Bi/Trigeminy.:	3/- beats
Max VEs/Hour...:	12.2 ending 12:40pm+

ST Segment Analysis

	CH1	CH2	CH3
Min ST Level:	-0.7mm	1.5mm	-0.2mm
Avg ST Level:	0.6mm	2.4mm	1.9mm
Max ST Level:	1.7mm	3.4mm	2.8mm
ST Episodes :	-	-	-

Supraventricular Ectopy

Total SVE Beats:	127
Atrial Runs....:	2
Beats.....:	12
Longest.....:	6 beats at 10:53pm
Fastest.....:	138 BPM at 11:03am
Atrial Pairs...:	5 events
Drop/Late.....:	1/1
Longest.....:	2.02 sec at 10:43pm
Single PAC's...:	105
Bi/Trigeminy.:	-/-
Max SVEs/Hour..:	13.2 ending 11:40pm

INTERPRETATION

NSR c PJs

Signed: _____ Date: _____

TRIAD

HOLTER MONITOR AND DIARY GUIDELINES

The purpose of monitoring you for 48 hours is to assess the effect of day to day activity on your heart. The holter monitor continuously records your heart's activity for the entire 48 hour period while you record your activities in a diary. In the TRIAD study we are interested in determining what physical as well as mental activities and emotional states lead to changes in your heart's activity and your ECG. A complete and accurate diary is necessary to determine if your ECG changes are related to physical activity, mental arousal and/or mood changes. The information we gather may be helpful in managing your heart disease. We appreciate your effort during this phase of TRIAD.

IMPORTANT TO REMEMBER:

1. Change the battery and cassette at: _____.

2. Your 48 hours of monitoring ends at: _____.

3. Be sure to bring both diaries, the tapes, the monitoring unit, the wrist watch and the activity monitor to your debriefing session on _____ at _____.

4. When the 48 hours of monitoring is done, or if your condition worsens during the monitoring, take the medications your doctor has prescribed for you and contact the research team.

5. If you have any question about the monitoring unit or the diary, please call!

Maralyn Fryberger
Study Nurse
(703) 299-1932 (pager)

Mark O'Callahan
Research Coordinator
Phone: (301) 295-9663

If you have filled out your diary correctly, we should be able to tell how you spent your day, how you felt while you engaged in you activities, whether you had any significant moods and emotions, and if so, when they occurred. Remember, that the diary should be comprehensive enough for us to reconstruct your prior day from the entries, **and the time of the recordings must be accurate.**

During the "debriefing" session the next day, we will go over your entries. At that time, we may ask detailed questions regarding specific entries (e.g., where were you at the time?), or you may wish to make specific comments, particularly about important aspects of activities not assessed by the structured diary format. With this in mind, we encourage you to jot down any useful reminders on the pages of your diary.

Date: _____

ID Number: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1.
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2.
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3.
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4.
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5.
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8.
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9.
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11.

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12.

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13.

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14.

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15.

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16.

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17.

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18.

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19.

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20.

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

22.

0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

23.

0 I can work about as well as before.
1 I take extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

24.

0 I haven't lost or gained much weight, if any, lately.
1 I have lost or gained more than 5 pounds.
2 I have lost or gained more than 10 pounds.
3 I have lost or gained more than 15 pounds.

I am purposely trying to loose or gain weight.
Yes____ No_____

25.

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

Items 1-21 are from BDI-II
Items 22-25 are from BDI-I

ID Number_____

Cook-Medley Scale

Read each statement and decide whether each is true as applied to you or false as applied to you. If a statement is true or mostly true, as applied to you, put an X in the column headed T. If a statement is false or not usually true, as applied to you, put an X in the column headed F. If a statement does not apply to you or if it something you do not know about, make no mark.

Remember to give your own opinion of yourself. Do not leave any spaces blank if you can avoid it.

	T	F	
1.	—	—	When someone does me wrong I feel I should pay him back if I can, just for the principle of the thing.
2.	—	—	I prefer to pass by school friends, or people I know but have not seen for a long time, unless they speak to me first.
3.	—	—	I have often had to take orders from someone who did not know as much as I did.
4.	—	—	I think a great many people exaggerate their misfortune in order to gain the sympathy and help of others.
5.	—	—	It takes a lot of argument to convince most people of the truth.
6.	—	—	I think most people would lie to get ahead.
7.	—	—	Someone has it in for me.
8.	—	—	Most people are honest chiefly through fear of being caught.
9.	—	—	Most people will use somewhat unfair means to gain profit or an advantage rather than to lose it.
10.	—	—	I commonly wonder what hidden reason another person may have for doing something nice for me.
11.	—	—	It makes me impatient to have people ask for my advice or otherwise interrupt me when I am working on something important.
12.	—	—	I feel that I have often been punished without cause.
13.	—	—	I am against giving money to beggars.
14.	—	—	Some of my family have habits that bother and annoy me very much.

	T	F	
15.	—	—	No one cares much what happens to you.
16.	—	—	My relatives are nearly all in sympathy with me.
17.	—	—	My way of doing things is apt to be misunderstood by others.
18.	—	—	I don't blame anyone for trying to grab everything he can get in this world.
19.	—	—	Most people make friends because friends are likely to be useful to them.
20.	—	—	I am sure I am being talked about.
21.	—	—	I am likely not to speak to people until they speak to me.
22.	—	—	Most people inwardly dislike putting themselves out to help other people.
23.	—	—	I tend to be on my guard with people who are somewhat more friendly than I had expected.
24.	—	—	I have sometimes stayed away from another person because I feared doing or saying something that I might regret afterwards.
25.	—	—	People often disappoint me
26.	—	—	I like to keep people guessing what I'm going to do next.
27.	—	—	I frequently ask people for advice.
28.	—	—	I am not easily angered.
29.	—	—	I have often met people who were supposed to be experts who were no better than I.
30.	—	—	I would certainly enjoy beating a crook at his own game.
31.	—	—	It makes me feel like a failure when I hear of the success of someone I know well.
32.	—	—	I have at times had to be rough with people who were rude or annoying.
33.	—	—	People generally demand more respect for their own rights than they are willing to allow for others.

	T	F	
34.	—	—	There are certain people whom I dislike so much that I am inwardly pleased when they are catching it for something they have done.
35.	—	—	I am often inclined to go out of my way to win a point with someone who has opposed me.
36.	—	—	I am quite often not in on the gossip and talk of the group I belong to.
37.	—	—	The man who had the most to do with me when I was a child (such as my father, stepfather, etc.) was very strict with me.
38.	—	—	I have often found people jealous of my good ideas, just because they had not thought of them first.
39.	—	—	When a man is with a woman he is usually thinking about things related to her sex.
40.	—	—	I do not try to cover up my poor opinion or pity of a person so that he won't know how I feel.
41.	—	—	I have frequently worked under people who seem to have things arranged so that they get credit for good work but are able to pass off mistakes onto those under them.
42.	—	—	I strongly defend my own opinions as a rule.
43.	—	—	People can pretty easily change me even though I thought that my mind was already made up on a subject.
44.	—	—	Sometimes I am sure that other people can tell me what I am thinking.
45.	—	—	A large number of people are guilty of bad sexual conduct.
46.	—	—	In a new job, I want to know who to get next to.
47.	—	—	Strangers look at me critically.
48.	—	—	I can be friendly with people who do things which I consider wrong.
49.	—	—	It is safer to trust nobody.
50.	—	—	I do not blame a person for taking advantage of someone who lays himself open to it.

Activity and Mood Questionnaire

(completed by patient at baseline and follow-up)

Patient ID_____ Date _____

In this section of the questionnaire you will be asked to indicate your usual frequency of several types of activities, moods, and emotions. You will also be asked to indicate how often you experience each item.

Below is an example of how the form might look after you complete it.

How often do you:	5 or more /day	2-4 /day	once /day	5-6 /wk	2-4 /wk	once /wk	1-3 /mo	4-12 /yr	1-3 /yr	Less than once/ year or never	On average, how much each time?	How many times in the past week?
Drink beer?					✓						2 bottles /cans	3
Drink wine?									✓		1 glasses	0
Drink liquor?										✓	0 glasses/ shots	0

If you have any questions with completing this form please ask your research nurse for assistance.

Thank you for the time and considerations you are giving this task. Your input is extremely valuable, and your effort will contribute immeasurably to our knowledge about cardiac arrhythmias and how better to treat, teach and learn from people who live with implantable cardioverter defibrillators.

Before you fill out the next page, please review the following list of levels of physical activity. Eight levels are shown with examples given in each category.

1	**Sleeping/Reclining**	sunbathing, lying on couch watching TV
2	**Sitting**	eating, reading, deskwork, sitting watching TV, highway driving
3	**Very light exertion**	office work, city driving, personal care, standing in line, strolling in a park
4	**Light exertion with normal breathing**	mopping, slow walking, bowling, sweeping, golfing with a cart, gardening with power tools
5	**Moderate exertion with deep breathing**	normal walking, golfing on foot, slow biking, downhill skiing, raking leaves, cleaning windows, interior painting, slow dancing, light restaurant work
6	**Vigorous exertion with panting; overheating**	slow jogging, tennis, swimming, x-country skiing, shoveling snow, fast biking, mowing with a push mower, heavy gardening, climbing up/down a ladder, softball, laying bricks, hurried heavy restaurant work
7	**Heavy exertion with gasping; much sweating**	running, fast jogging, pushing a car stuck in snow, changing tires, shoveling heavy or deep snow, competitive basketball, putting down wall-to-wall carpet, ladder or stair climbing with a 50 lb. load
8	**Extreme or peak exertion**	sprinting, fast running, fast jogging or jogging uphill, pushing and pulling with all your might, unusually extreme work

Now, for each level of physical activity listed below, place a checkmark in one of the boxes which represents how often you exert yourself to that level and what kinds of activities you usually do at that level. *Consider the time interval since the device was implanted or the time interval since you last completed this form.* In the last two columns, please indicate 1) how many times in the past week you achieved each level of activity and 2) how much time on average you spend doing the activity, each time you do it.

		5 or more /day	2-4/ day	once /day	5-6/ wk	2-4/ wk	once /wk	1-3/ mo	4-12 /yr	1-3 /yr	Less than once/ yr or never	What activity do you usually do?	Number of times in past week?	How long each time?
8	Extreme													
7	Heavy													
6	Vigorous													
5	Moderate													
4	Light													

1. How many city blocks do you walk each day (1 mile= 10 blocks)? _____blocks

2. What is your usual pace of walking? ☐ casual strolling ☐ average or normal
☐ fairly brisk ☐ striding

3. How many flights of stairs do you climb each day (10 steps=1 flight)? _____flights

Before you fill out the next grid, please review the following seven levels of anger which people experience.

1	**Calm**	
2	**Busy, but not hassled**	
3	**Mildly angry, irritated and hassled**	but it does not show
4	**Moderately angry**	so hassled it shows in your voice
5	**Very angry**	body tense, clenching fists or teeth
6	**Furious**	almost out of control, very angry, pounding table, slamming door
7	**Enraged**	you've lost control, throw objects, hurting yourself or others

Now, for each level of anger listed below, place a checkmark in one of the boxes which represents the frequency with which you experience that level of anger. *Consider the time interval since the device was implanted or the time interval since you last completed this form.* In the last two columns, please indicate 1) how many times in the past week you achieved each level of anger and 2) how much time on average you spend at that level, each time you do it. (Please write "0" if you have not experienced a particular level of anger.)

		5 or more /day	2-4/ day	once /day	5-6 /wk	2-4/ wk	once /wk	1-3 /mo	4-12 /yr	1-3/ yr	Less than once/yr or never	Number of times in past week?	How long each time?
7	**Enraged**												
6	**Furious**												
5	**Very angry**												
4	**Moderately angry**												
3	**Mildly angry**												

Before you fill out this page, please review the following levels of anxiety which people experience.

1	**Mildly tense**	worried or preoccupied
2	**Moderately tense**	restless, keyed up, upset
3	**Very tense**	worries interfering with sleep or concentration
4	**Extremely tense**	fear or panic, periods of shaking, dizziness, or intense distress

Now, for each level of anxiety listed below, place a checkmark in one of the boxes to the right which represents the frequency with which you experience these levels of anxiety. *Consider the time interval since the device was implanted or the time interval since you last completed this form.* In the last two columns, please indicate 1) how many times in the past week you achieved each level of anxiety and 2) how much time on average you spend at that level, each time you do it. (Please write "0" if you have not experienced a particular level of anxiety.)

		5 or more /day	2-4/ day	once /day	5-6 /wk	2-4 /wk	once /wk	1-3 /mo	4-12 /yr	1-3 /yr	Less than once/ yr or never	Number of times in past week?	How much each time?
4	**Extremely tense**												
3	**Very tense**												
2	**Moderately tense**												
1	**Mildly tense**												

In this section, we ask about use of alcohol, caffeine, cocaine, or amphetamines and cough, cold, or allergy medicines. Please place a checkmark in the box which represents the frequency with which you use each of the items listed below. Then, please indicate how many times in the past week you used each of the items.

How often do you?	5 or more /day	2-4/ day	once /day	5-6 /wk	2-4 /wk	once /wk	1-3 /mo	4-12 /yr	1-3 /yr	Less than once/yr or never	On average, how much each time?	Number of times in past week?
drink beer?											_____bottles/cans	
drink wine?											_____ glasses	
drink liquor?											_____glasses/shots	
drink coffee with caffeine?											_____cups	
drink tea with caffeine?											_____cups	
drink cola with caffeine?											_____cups	
use cocaine or amphetamines?												
use cough, cold, or allergy medicines, or diet pills?											What products do you use? _____ _____	
eat a meal so large that you feel bloated?												

Smoking:

	Yes	No
1. Did you ever smoke cigarettes, cigars, pipes?	☐	☐

	Yes	No
2. Do you currently smoke?	☐	☐

If no, how long ago did you quit?_____
If yes, how much do you currently smoke?

_____ cigarettes/day
_____ cigars/day
_____ pipes/day

In this section, we ask about sexual intercourse and exposure to extremes of temperatures. Please place a checkmark in the box which best represents the frequency with which you experience each item. *Consider the time interval since the device was implanted or the time interval since you last completed this form.* In the last two columns, please indicate 1) how many times in the past week you experienced each item and 2) how much time on average you spend in each activity, each time you do it.

How often?	2-4 /day	once /day	5-6 /wk	2-4 /wk	once /wk	1-3 /mo	4-12 /yr	1-3 /yr	Less than once/ yr or never	Number of times in past week?
do you engage in sexual intercourse?										
have you been so cold that you are shivering or have goose bumps?										
have you been so hot that you are sweating or are feeling overheated?										